May 13, 2016

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

The following statement is submitted on behalf of People for the Ethical Treatment of Animals (PETA) in response to the March 18, 2016 Federal Register Notice by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). Our comments below are related to the development and use of nonanimal test methods that are relevant to the ICCVAM mission and current activities.

Comments on Current Activities

- We appreciate the effort that National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and ICCVAM members have invested in coordinating workshops, webinars, and other events that bring together industry, government, academia, and non-governmental organizations. We look forward to continued momentum to bring stakeholders together to discuss the implementation of approaches that reduce and replace animal testing. We hope to see less involved ICCVAM member agencies become more engaged in these workshops and efforts from all agencies to implement relevant recommendations to reduce animal use.

- We commend NICEATM and the Environmental Protection Agency's (EPA) Office of Pesticide Products for their ongoing work to significantly reduce the use of animals in the "6-pack" of acute toxicity tests for pesticide products. We were pleased to see that the EPA recently issued final guidance on an approved process for establishing and implementing alternative approaches to *in vivo* acute toxicity studies and draft guidance to waive dermal toxicity tests when acute oral data are available for pesticide formulations. The EPA and NICEATM also are conducting comparative analyses of parallel *in vitro* and historical *in vivo* data on acute eye irritation and skin sensitization to confirm the appropriateness of available nonanimal methods for use with pesticides. Furthermore, the EPA is working to expand its policy on the use of a nonanimal framework for the classification of eye irritation potential of pesticide products to a larger chemical space. In place of conducting new animal tests, the EPA has also initiated a pilot to accept existing oral and inhalation toxicity data paired with calculations using the GHS Mixtures Equation to classify pesticide formulations. In an effort to facilitate the use of nonanimal methods, the EPA is exploring an eventual transition from its current

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classification and labeling system to the GHS classification system. The EPA has increased the transparency of its efforts and encouraged collaboration and feedback by hosting regular discussions with industry and other interested stakeholders. We hope that the EPA will continue to work with industry to ensure that the policies to reduce animal use are implemented by industry. In addition, we look to other ICCVAM member agencies to use the EPA's process as an example for implementing nonanimal approaches within their own agencies.

- We commend NICEATM and ICCVAM's activities with industry and with the EPA to coordinate online databases of *in vitro* and historical *in vivo* data for the rodent uterotrophic bioactivity; the Federal Insecticide, Fungicide, and Rodenticide Act six-pack; ocular irritation; developmental toxicants; and inhalation toxicity. Databases such as these facilitate efforts to validate alternative test methods. As a result of this work, the EPA decided to no longer require the *in vivo* uterotrophic assay under the Endocrine Disruption Screening Program Tier 1 testing when estrogen pathway high throughput *in vitro* assay data are available.

- We are pleased to see funding opportunities in nonanimal methods, such as the Small Business Innovation Research Phase IIB Awards for Validation and Commercialization of Approaches to Reduce Animal Use in Toxicology Testing offered by NIEHS; the Transform Tox Testing Challenge offered by EPA/NIEHS/NIH; and the DREAM Toxicogenetics Collaboration organized by scientists from NIEHS, the NIH's National Center for Advancing Translational Sciences, and others. We hope to see these funding opportunities continued and expanded, and encourage ICCVAM to coordinate with member agencies on the development of a publically-available system that tracks the amount of funding, progress, outcomes, and applications of the funded projects. This, along with reporting member agencies' funding of nonanimal methods in relation to animal tests, would help to ensure the efficient use of limited federal funding, continuity and application of project outcomes, and agencies' commitment to modern toxicity test methods.

Comments on ICCVAM's Mission

- *Reviewer training*: We continue to see an urgent need for training of regulatory agency reviewers and USDA APHIS inspectors and veterinary medical officers (VMOs). Industry is reporting variability in the acceptance of nonanimal methods among reviewers and is reluctant to use *in vitro* and *in chemico* methods when uncertainty exists in their acceptance or if their use incurs delays in product registration due to reviewer unfamiliarity with nonanimal methods. We encourage ICCVAM member agencies to organize trainings on nonanimal test methods and to implement a system for expedited review of data submissions utilizing nonanimal test methods as an incentive for using nonanimal methods. PETA has already collaborated with *in vitro* and *in silico* experts to organize such trainings for the EPA, and we welcome the opportunity to do so for other agencies.

- *Fostering international harmonization*: We have previously emphasized the need for harmonization of nonanimal methods across countries and across standard organizations (such as the U.S. Pharmacopeia and the International Standards Organization). Without global harmonization, animal use will not be significantly reduced. We are happy to see diversity in this year's ICCVAM public forum speakers. We encourage ICCVAM to incorporate additional groups into International Cooperation on Alternative Test Methods (ICATM) meetings and to

urge representatives from various standards organizations to attend ICCVAM public forum and Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) meetings so that they are kept informed of changing regulatory requirements that need to be addressed in their own respective guidance documents. Additionally, we encourage ICCVAM to work with member agencies to accept the use of nonanimal methods already accepted in other countries, such as the consistency approach in batch testing for biologics and skin and eye testing.

- *Quantifying animals used in testing*: We continue to urge ICCVAM to quantify the numbers of animals used in testing by working with the NIH to regularly publish the numbers of all animals, including mice and rats, used in NIH-funded laboratories; to work with industry to collect and publish the numbers of mice and rats used for both regulatory and non-regulatory purposes; and to engage its member agencies to collect and publish the numbers of mice and rats used in-house. We encourage ICCVAM to work with the NIH and the USDA to help the U.S. join other countries, such as those in the E.U., that publish the numbers of animals used in testing and the endpoints for which they were used. This reference point is the only way to fully monitor U.S. progress towards the replacement of animals in testing.

- *Tracking the use of nonanimal methods*: Nonanimal methods are increasingly being accepted by regulators, but this is not reliably translating to their use by industry. For example, the EPA accepts the use of an alternate testing framework for classification of eye irritation potential of antimicrobial cleaning products. However, very few product submissions have used the alternate framework since its implementation. Additionally, there are a number of accepted nonanimal methods and recommendations in the area of biologics testing with unknown implementation, such as *in vitro* and serological replacements for *in vivo* challenge assays; USDA Center for Veterinary Biologics (CVB) Notice 12-12 on assessment of the use of humane endpoints, analgesia, and anesthesia for intracerebral challenge and other challenge procedures; CVB Memorandum 800.116 on waiving target animal batch safety testing; and CVB Notice 15-13 on the option to remove back-titration hamsters *from in vivo* potency tests for *Leptospira* serogroups *Canicola* and *Icterohaemorrhagiae*. We encourage ICCVAM to work with member agencies to track the implementation of alternatives and agency recommendations, which is imperative to monitor the use of nonanimal methods, and in cases where there has not been uptake of a method, it provides an opportunity to work with member agencies and industry to overcome obstacles to its use.

- *Increased dialogue*: Fostering a culture of dialogue on product testing plans between companies and their regulatory agencies will increase the use of nonanimal test methods. Such dialogue should include discussions on the use of nonanimal test methods, and, when *in vivo* testing is required, the benefit of conducting parallel nonanimal testing to build data for validation efforts and help companies become familiar with conducting nonanimal test methods. For example, the recent workshop report, "Alternatives to HIST for acellular pertussis vaccines: progress and challenges in replacement", encourages applicants to engage reviewers prior to the submission of data from alternative methods (Arciniega et al, 2016. *Pharmeuropa Bio&SN*. pp. 82-96). Companies and reviewers can gain from constructive dialogue on the potential use of nonanimal test methods in specific applications prior to conducting testing.

Thank you for the opportunity to submit our comments. We are happy to see NICEATM and ICCVAM's continued efforts to reduce animal testing, and hope to see further commitment from less

engaged agencies in the coming year. We look forward to working with you on current and future initiatives.

Sincerely,

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