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Sent via email to [whiteld@niehs.nih.gov](mailto:whiteld@niehs.nih.gov)

Dear Dr. White,

The following comments are submitted on behalf of People for the Ethical Treatment of Animals (PETA) in response to the August 19, 2016 Federal Register Notice by the National Institutes of Health (NIH), “Scientific Advisory Committee on Alternative Toxicological Methods; Announcement of Meeting; Request for Comments.” The preliminary meeting agenda outlined topic areas for public comments and the SACATM 2016 meeting background document “[A Strategy for Implementing the Vision for Toxicity Testing in the 21st Century](#)” (“Background Document”) posed specific discussion questions. Our responses below are divided among agenda sections.

### **Report on ICCVAM and NICEATM Activities**

The ICCVAM Biennial Progress Report 2014-2015 provided an accounting of the progress achieved by ICCVAM, NICEATM, and member agencies toward establishing animal-free approaches to toxicity testing. We are pleased to see the many and varied activities undertaken during the reporting period including development and validation of *in vitro* and *in silico* methods; comparative analyses of *in vitro/in vivo* data; participation in webinars, workshops, and scientific meetings; international collaboration; and outreach efforts. With the new philosophy adopted in 2013 and the dedication and enthusiasm of current leadership, ICCVAM and NICEATM are making strides toward replacing animal use.

### **Perspective on National Toxicology Program and National Research Council Reports on Toxicity Testing in the 21<sup>st</sup> Century: How Far Have We Come?**

The National Research Council’s 2007 report *Toxicity Testing in the 21st Century: A Vision and a Strategy* set the stage for using modern human cell-based, animal-free methods that are more predictive of human health outcomes. We have been encouraged by the investment in and development of numerous non-animal methods since the publication of the report, but continue to see a need for timely adoption of new test methods by regulatory agencies. We ask that SACATM encourage ICCVAM member agencies to rapidly adopt clear guidance on the acceptance—and preference—for non-animal methods and to ensure that reviewers know how to interpret data from the new methods. Our [comments for the 2015 SACATM meeting](#)

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provided several examples of agencies failing to update guidance to clearly note that non-animal methods, such as for skin sensitization and eye and skin irritation, are accepted or preferred over the animal tests.

We request that SACATM encourage regulatory agencies to form collaborative partnerships with other regulatory agencies, industry, and non-governmental organizations (NGOs) on validation efforts when they see a need for further data on the predictive value of non-animal methods in a specific chemical space. For example, the EPA Office of Pesticide Program's collaboration with industry and an independent *in vitro* laboratory led to the development of an [alternate framework for assessing the eye irritation potential](#) of anti-microbial cleaning products that does not rely on the Draize rabbit test. This work is currently being extended to conventional pesticides with the help of NGOs and industry members that have provided side-by-side *in vivo* and *in vitro* eye irritation data, which facilitates a comparative retrospective analysis. Our organization would be happy to help plan and oversee similar validation efforts in the future.

As is required in the E.U., it is critical that U.S. agencies begin to require the use of available non-animal alternatives rather than continuing to accept animal tests. The recently enacted Frank R. Lautenberg Chemical Safety for the 21st Century Act reforms the way chemicals are regulated in the U.S. For the first time, both regulators and industry are required to develop new hazard information using alternative test methods that reduce and replace the use of animals while providing information of better scientific quality and relevance. As a federally chartered interagency advisory committee on the development, validation, and acceptance of alternative test methods, SACATM should participate actively in the development of EPA OPPT's statutorily-mandated strategic plan to promote alternative test methods. SACATM can then ensure that the spirit of this historic legislation is applied to the fullest extent possible not only by EPA OPPT but by other offices within EPA and other agencies in their future rulemaking and guidance to industry.

### **ICCVAM Roadmap for Skin Sensitization Testing**

Substantial progress has been made in the development of multiple integrated approaches to testing and assessment of skin sensitization hazard. There are currently three Organisation for Economic Cooperation and Development (OECD) approved and validated *in vitro* or *in chemico* methods available for use. In addition, ICCVAM and NICEATM have worked on the development of an open source Bayesian network approach and development of QSAR models to identify potential skin sensitizers. The EPA OPP also is involved in comparative analysis of *in vitro/in vivo* data with respect to predicting the skin sensitization hazard of pesticides.

The positive results of these efforts and the proven ability of the *in vitro/in chemico methods* to accurately predict human outcomes show that it is time for ICCVAM member agencies to adopt them. Agencies should update guidance to clearly indicate that these methods are accepted or, better yet, preferred over the animal tests. Along with adoption, there must be training of regulatory reviewers in use of these methods and interpretation of data. Also, industry and contract research laboratories should be made aware of the acceptance of new methods—our organization is happy to assist in this effort. Based on the proven effectiveness of the non-animal skin sensitization methods, we urge SACATM to develop a roadmap that lays out a fast track for adoption by member agencies.

## Moving Away from Animals for Toxicity Testing

The Background Document touches upon the problems associated with traditional approaches to validation, which often rely on comparing data from non-animal tests to animal tests that were never validated for their relevance to humans. Increased access to existing data, including negative results, will substantially help advance the validation of non-animal strategies. For example, work on developing acute toxicity testing alternatives is being accelerated by EPA OPP giving NICEATM access to pesticide data collected under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

Also key to a toxicity testing paradigm should be an understanding of mechanisms of toxicity. Adverse outcome pathways (AOPs) are important in the design of non-animal testing strategies and more resources should be dedicated to examining existing data for the creation of AOPs.

In addition, periodic review of how data from currently required animal tests are being applied will help to reduce the use of animals in testing. For example, the one-year chronic toxicity test in dogs traditionally required for pesticide registration has been eliminated in many countries, starting with the U.S. in 2007, after retrospective analyses showed the data were rarely used for setting exposure limits. A similar review (Billington et al. 2010)<sup>1</sup> calls for the elimination of the mouse carcinogenicity study, which has been shown to have contributed little or nothing to either derivation of an acceptable daily intake (ADI) for assessment of chronic risk to humans or hazard classification for labelling purposes.

### Coordinating Activities between the Federal Government and Stakeholders

The Background Document asks what strategies and mechanisms could be employed to increase communication and coordination of activities amongst and between the federal government and key stakeholders. We recommend:

- *Formation of stakeholder groups:* The EPA OPP set an example for developing a transparent forum for the agency and its stakeholders when it created the Acute Toxicity Alternatives Stakeholder Group. In collaboration with its stakeholders, OPP has established goals for adopting alternatives to acute toxicity testing and is giving regular updates to the stakeholder group. The forum provides a feedback mechanism for industry and NGOs to provide comments, give advice, and participate in workgroups that deal with specific issues. We recommend OPP's stakeholder group be used as a model for other ICCVAM member agencies.
- *Formation of a center dedicated to replacement and reduction of animal testing:* We are happy to see that SACATM is promoting the development of a comprehensive strategy to reduce the use of animals in toxicity testing. We ask that this strategy address the pathways to adoption of test methods by federal agencies and industry. The Background Document highlights changes in policy, practice, and regulation that may be necessary to implement a system based in modern toxicological methods and which cannot adequately be addressed by any single agency or existing government entity. We support the suggestion that the

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<sup>1</sup>Billington R, Lewis RW, Mehta JM, Dewhurst I. 2010. The mouse carcinogenicity study is no longer a scientifically justifiable core data requirement for the safety assessment of pesticides. *Crit Rev Toxicol*, 40(1):35-49.

Office of Science and Technology Policy charge a workgroup with drafting a roadmap for implementing the NRC vision in *Toxicity Testing in the 21<sup>st</sup> Century* and another workgroup to forward the roadmap and assist the National Academy of Sciences in convening a series of workshops or panels to forward progress. These efforts would benefit from the establishment of a center dedicated to replacing and reducing animal testing and serving as a focal point for method validation and training. Such a center would improve the efficiency of validation and training efforts by various agencies and would provide a point of contact for improved collaboration with E.U. activities.

- *Workshops*: In the past year, the PETA International Science Consortium coordinated a productive [workshop](#) with NICEATM on replacing the *in vivo* acute systemic toxicity test methods, an ICCVAM priority area. Some ICCVAM member agencies attended and presented at this meeting. Progress has been made and work is ongoing to implement the expert recommendations from this workshop. However, we noted in our [2015 SACATM comments](#) that there is a need for updates on progress toward the recommendations set forth in other workshops organized by ICCVAM (e.g., by FDA on the 2011 rabies workshop).
- *NICEATM as Intermediary for Data Sharing*: As mentioned above, data sharing advances validation of non-animal strategies, and NICEATM has been a valuable player as a third-party partner to confidentially collect data. We ask that SACATM encourage ICCVAM member agencies to share data with NICEATM as the EPA OPP has done with its FIFRA data for the “six pack” of toxicity endpoints.

### **Impediments to Adoption of Alternative Approaches**

Although the EPA OPP has accepted the use of certain alternatives to the Draize eye irritation test when registering new antimicrobial cleaning products<sup>2</sup> since 2013, only a small number of these products have been registered since then using the alternatives. In a recent publication<sup>3</sup>, we identify several impediments that have contributed to industry’s limited use of these alternatives, which are applicable on a larger scale to ICCVAM member agencies. These include (1) lack of full regulatory acceptance within U.S. federal and state agencies; (2) uncertainty by industry over regulatory reviewers’ awareness of and proficiency with non-animal methods that could lead to longer review times or rejection of registration submissions; (3) lack of harmonization of methods across countries and across standards-making organizations; and (4) differences between OPP’s hazard categories and the Globally Harmonized System’s (GHS) categories which the alternative methods were designed to predict.

These factors will impact the adoption of other alternative approaches in the future as well if not addressed now. We suggest SACATM advise ICCVAM member agencies to take actions to overcome these impediments, such as:

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<sup>2</sup>Alternate Testing Framework for Classification of Eye Irritation Potential of EPA-Regulated Pesticide Products. Available: <https://www.epa.gov/pesticide-registration/alternate-testing-framework-classification-eye-irritation-potential-epa>

<sup>3</sup>Clippinger AJ, Hill E, Curren R, Bishop PL. 2016. [Bridging the gap between regulatory acceptance and industry use of non-animal methods](#). *ALTEX*, doi: 10.14573/altex.1601311.

- Develop leadership within the regulatory agency and the regulated industry to overcome institutional inertia and promote collaboration among motivated groups of people;
- Create incentives for industry to use new methods, such as expedited reviews of data packages;
- Provide training for regulatory agency reviewers to ensure that data from new methods are properly and efficiently handled;
- Encourage federal regulators to promote use of alternatives at international forums to drive other countries to accept these methods;
- Transition to use of GHS in all federal and state agencies;
- Review arbitrary animal test hazard category cut-off values and modify prediction algorithms for non-animal tests where necessary;
- Expand outreach to industry;
- Create systems to monitor use of new methods, such as tracking the number of regulatory submissions using alternative approaches, and provide feedback on any remaining issues contributing to lack of use;
- Incorporate additional groups into International Cooperation on Alternative Test Methods (ICATM) meetings and urge representatives from various standards organizations to attend ICCVAM public forum and SACATM meetings so that they are kept informed of changing regulatory requirements that need to be addressed in their own respective guidance documents.

### **Promoting Adoption of Alternative Testing Strategies**

We recommend that SACATM encourage ICCVAM member agencies to take immediate action to promote the adoption of alternative testing strategies by:

- providing regular training opportunities for their reviewers on non-animal testing policies, methods, and data interpretation. While some agencies have been actively engaged in training sessions, other agencies have not. PETA can help to coordinate presentations from experts on the growing number of alternative testing strategies, as we have had success sponsoring such presentations in the past.
- sharing a current list of validated alternative methods so that reviewers and industry are aware of, and are using, available alternatives.
- allowing access to USDA’s Category E justifications as well as an ability to search the reports. It is not uncommon for Category E justifications, submitted by USDA-registered facilities in an annual report, to state that alternatives are not available even when alternatives exist. The USDA recently launched its new “Animal Care online search tool”. Currently, this tool does not provide access to Category E justifications.
- monitoring the submission of non-animal and animal data to see where replacement efforts have been successful and where additional efforts should be focused.
- publishing the numbers of animals of *all* species (including mice, rats, birds, and cold-blooded animals) used to test specific endpoints, as is done in the United Kingdom. Without this information, the U.S. is unable to monitor progress towards the replacement of animals in testing.

Additional details on these points can be found in our [2015 SACATM comments](#).

We looked forward to a continued productive relationship with NICEATM and ICCVAM and are happy to assist in any way we can to help reduce animal use. Please feel free to contact me with any comments or questions.

Kind regards,

Signature redacted

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