



September 11, 2017

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Dear Dr. Wolfe,

The following comments are submitted on behalf of People for the Ethical Treatment of Animals (PETA) in response to the Federal Register Notice of August 14, 2017, by the National Institutes of Health, “Scientific Advisory Committee on Alternative Toxicological Methods; Announcement of Meeting; Request for Comments.” Our comments on the preliminary meeting agenda topics are below, and they expand on our [comments](#) on the Interagency Coordinating Committee on the Validation of Alternative Methods’ (ICCVAM) strategic roadmap that were submitted to the May 2017 ICCVAM public forum.

### **Strategic Goal: Encourage Adoption and Use of New Approaches by Federal Agencies and Regulated Industries**

As noted in our 2016 Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) [comments](#), given the lack of a federal statute that specifically requires the use of alternatives to animal tests when they exist, regulatory agencies must adopt clear language on the acceptance of—and preference for—non-animal methods. Frequently, the status of regulatory acceptance of specific methods is unclear, especially to smaller companies. The U.S. Environmental Protection Agency (EPA) Office of Pesticides Program (OPP) has made great strides in informing industry and other stakeholders of its acceptance of non-animal approaches and its ongoing efforts in this area via its [webpage](#) titled “Strategic Vision for Adopting 21<sup>st</sup> Century Science Methodologies,” which also contains related guidance documents. The development of similar centralized repositories by other ICCVAM member agencies would help eliminate confusion surrounding the acceptance of non-animal test methods and strategies.

In addition, such sources of information would allow industry to remain informed about progress made following ICCVAM workshops. For example, in previous ICCVAM [comments](#) and SACATM [comments](#), we noted that recommendations put forth during international workshops co-organized

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by ICCVAM and NICEATM on the use of alternative methods in the development and testing of biologics have great potential to reduce animal use or suffering, but very little has been published on the agencies' progress toward fulfilling the recommendations. In cases in which agencies did respond to workshop recommendations by changing testing policies, they do not appear to be promoting or tracking the use of alternative approaches. Without this information, it is impossible to identify and overcome the barriers that keep companies from adopting these alternative approaches. In some instances, these barriers have persisted for many years despite having been discussed in previous biologics workshops cosponsored by agencies.

Even when industry is aware of the regulatory acceptance of a non-animal method, numerous impediments can dissuade industry from using them.<sup>1</sup> As an example, the use of alternative approaches could lead to longer review times or even rejection of registration submissions if reviewers are not aware of new policies and how to interpret data from non-animal methods. To address this issue, we encourage SACATM to help ICCVAM agencies find ways to foster the adoption of non-animal methods, including expedited review of data packages containing non-animal tests. Agencies must also ensure that reviewers have the time and resources to become proficient in interpreting data from new methods. This can be facilitated by training opportunities on *in vitro* or *in silico* methods; workshops and webinars; and factsheets, tutorials, and videos on these approaches. The PETA International Science Consortium Ltd. and other organizations have organized training opportunities and developed educational resources that can be used, and we would be happy to assist agencies in developing and implementing training programs.

### **How Will ICCVAM Measure the Strategic Roadmap's Success?**

The development of predictive animal-free test methods does not necessarily translate into their adoption by industry and regulators. To monitor the successful implementation of non-animal strategies, the roadmap should recommend a path for ICCVAM member agencies to report information on animal testing. This reporting could include various types of information, such as the following: (1) the number of animals used per endpoint; (2) the number of *in vitro* tests that are submitted versus the number that are accepted per endpoint; (3) the number of *in vitro* tests that are submitted versus the number of animal tests that are submitted per endpoint; or (4) the number of waivers granted versus the number of required studies (as is done by the OPP for some endpoints on slide 4 [here](#)).

### **Strategic Goal: Use of Timely, Flexible, and Robust Practices to Establish Confidence in New Methods**

#### **Establishing Confidence**

Regulatory agencies can establish confidence in new methods and increase their adoption by actively facilitating and participating in validation efforts. We encourage SACATM to help agencies implement streamlined validation processes that encourage the timely implementation and acceptance of human-predictive approaches for toxicity testing. Because of the variability and questionable predictivity of animal data, the validation of non-animal methods should not

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<sup>1</sup>Clippinger AJ, Hill E, Curren R, Bishop PL. 2016. [Bridging the gap between regulatory acceptance and industry use of non-animal methods](#). *ALTEX*. 33(4):453-458.

simply rely on concordance with animal data.<sup>2,3</sup> In the absence of human data, one suggested benchmark for evaluating *in vitro* methods is the concordance of animal data for the same chemicals that have been tested across multiple laboratories. For skin sensitization, this has been found to be indicative of the ability of animal tests to predict human health outcomes.<sup>4</sup>

When agencies see a need for further data on the predictive value of non-animal methods in a specific chemical space, they should form collaborative partnerships with other regulatory agencies, industry, and nongovernmental organizations (NGO) to undertake validation efforts. For example, the OPP's collaboration with industry and NGOs led to the development of an *in vitro* framework for assessing the eye irritation potential of anti-microbial cleaning products in place of the Draize rabbit test. This work is currently being extended to develop an *in vitro* testing strategy applicable to pesticide formulations. These efforts have used existing parallel *in vivo* and *in vitro* data, in addition to prospective *in vitro* testing.

To ensure that a non-animal method will be accepted after the successful completion of validation efforts, regulatory agencies that require or use data from an animal test that the method replaces should be involved in its validation from the onset. For example, the Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) recently finalized its [Medical Device Development Tools](#) program to qualify tools that can be used in the development and evaluation of medical devices. By tightly defining a new non-animal method's context of use, medical device sponsors can collaborate with CDRH on the design of a validation process to ensure that a successfully validated method will be able to be used without ambiguity. Similar tools within additional ICCVAM agencies would help increase the adoption of non-animal methods.

### **Use of Tissue Chip by FDA**

We are supportive of the FDA Center for Food Safety and Applied Nutrition's (CFSAN) partnership with Emulate, Inc., to evaluate the company's organ-on-a-chip technology for predicting the toxicity of potential chemical hazards found in new foods, cosmetics, and dietary supplements. There is also considerable support from the public for such partnerships, as demonstrated by PETA's collection of more than 40,000 signatures from people expressing their appreciation for CFSAN and Emulate's partnership. We ask that SACATM, NICEATM, and ICCVAM member agencies work to make additional resources available for such collaborations.

### **Data Sharing**

Data sharing advances the validation of non-animal strategies, and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) has been a valuable third-party partner for confidentially collecting data. The OPP has shared data for the "six pack" of toxicity endpoints with NICEATM, which will be added to [NICEATM's Integrated Chemical Environment](#). We ask that SACATM encourage the FDA, the EPA's Office of Pollution Prevention and Toxics, and other ICCVAM member agencies to also share data with NICEATM.

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<sup>2</sup>Kleinstreuer NC. 2017. [Skin sensitization update](#) [presentation]. Bethesda, Md.: ICCVAM Public Forum.

<sup>3</sup>Karmaus AL, Allen D, Kleinstreuer NC, Casey W. 2017. [Characterizing the variability of LD<sub>50</sub> values in acute toxicity studies: Implications for alternative methods development](#) [presentation]. Seattle: 10<sup>th</sup> World Congress on Alternatives and Animal Use in the Life Sciences.

<sup>4</sup>Kleinstreuer. 2017. [Skin sensitization update](#).

## **Strategic Goal: Connect End Users With the Development of New Tools**

SACATM should encourage ICCVAM member agencies and industry to collaborate with *in vitro* and *in silico* method developers to ensure that resources are spent developing methods that will be used by industry and fulfill the needs of regulatory agencies. Federal agencies such as CFSAN and the Department of Defense<sup>5</sup> have undertaken such collaborations, and further combined efforts between method developers and end users will help forward the use of promising technology and assist in modernizing test methods and strategies.

### **Implementation: Alternatives for Skin Sensitization Testing**

Non-animal testing strategies incorporating *in vitro*, *in chemico*, and *in silico* skin sensitization methods have shown greater predictive ability for human health outcomes than do animal tests.<sup>6</sup> There are currently three *in vitro* or *in chemico* methods available for use that are approved and validated by the Organisation for Economic Cooperation and Development (OECD) as well as two draft test guidelines. It is time that ICCVAM member agencies adopted these approved methods.

When agencies require additional validation for their specific chemical spaces, we urge them to fast-track such projects. For example, the International Organization for Standardization Technical Committee 194 working group 8 conducted a round-robin study to evaluate the use of reconstructed human epidermis in assessing the potential of medical device extracts to cause skin irritation.<sup>7</sup> SACATM should encourage CDRH to provide its regulatory reviewers with the necessary training immediately so that it can begin to accept the *in vitro* skin irritation method—and ask them to begin a similar round-robin effort for skin sensitization testing of device extracts. We encourage SACATM to work with ICCVAM agencies on efforts to implement existing non-animal methods as quickly as possible.

Globally, we are encouraged by the 2016 International Cooperation on Alternative Test Methods (ICATM) workshop on the international regulatory acceptance of non-animal approaches to skin sensitization testing, and we look forward to developments stemming from this event. ICCVAM member agencies should organize similar workshops relevant to their testing requirements, and PETA would be happy to offer its support for such endeavors.

### **Implementation: Alternatives for Acute Systemic Toxicity Testing**

We were pleased to see that the OPP continues to implement measures to reduce animal use for acute systemic toxicity testing of pesticide formulations, including its [GHS Mixtures Equation pilot program](#). Additionally, significant progress in implementing alternatives could be made if

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<sup>5</sup>Mowatt T. 2012. Wyss Institute to receive up to \$37 million from DARPA to integrate multiple organ-on-chip systems to mimic the whole human body. Available at: <https://wyss.harvard.edu/wyss-institute-to-receive-up-to-37-million-from-darpa-to-integrate-multiple-organ-on-chip-systems-to-mimic-the-whole-human-body/>

<sup>6</sup>Kleinstreuer. 2017. [Skin sensitization update](#).

<sup>7</sup>De Jong WH, Hoffmann S, Lee M, Kandarova H, Letasiova S, De La Fonteyne LJ, Pellevoisin C, Tornier C, Bremond C, Haishima Y, *et al.* 2017. Round robin study to evaluate the reconstructed human epidermis (RhE) model as *in vitro* skin irritation test for detection of irritant activity in medical device extracts [poster]. Baltimore: Society of Toxicology 56<sup>th</sup> Annual Meeting and ToxExpo.

the OPP transitioned from its current classification and labeling system to a “hybrid,” flexible form of the GHS classification system that would facilitate acceptance of acute *in vitro* test data. OECD non-animal methods are now developed to align with the GHS classification system, and the existence of a separate classification system delays the acceptance of new methods.

Efforts to increase the availability of non-animal methods for determining acute systemic toxicity are ongoing.<sup>8,9</sup> NICEATM, various ICCVAM member agencies, and the PETA International Science Consortium have jointly organized two workshops addressing alternative approaches to acute systemic toxicity testing in the past two years. Workshop proceedings are in preparation or have been published<sup>10</sup> and presented in public forums,<sup>11</sup> and working groups have been formed to implement the workshop recommendations. We look forward to continued collaboration with NICEATM, ICCVAM member agencies, and industry on this effort.

### **Implementation in Other Areas**

To conclude, we note that a full transition to a new, human-based toxicity testing paradigm is dependent on global use and acceptance of these methods. U.S. regulators, companies, and NGOs must collaborate with international partners to facilitate global modernization of testing requirements. In addition to webinars, workshops, and publications on these efforts, discussions within ICATM or at the OECD are useful for sharing information about non-animal methods.

We look forward to continued collaboration with SACATM, NICEATM, and ICCVAM member agencies, and are happy to assist in any way possible to help replace animal use. Please feel free to contact me with any comments or questions.

Kind regards,



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<sup>8</sup>Strickland J, Karmaus AL, Chang X, Paris M, Allen D, Kleinstreuer N, Casey W. 2017. [Correlation of \*in vitro\* cytotoxicity and acute toxicity](#) [presentation]. Seattle: 10<sup>th</sup> World Congress on Alternatives and Animal Use in the Life Sciences.

<sup>9</sup>Lowit A, Schlossenger C, Myska A, Patlewicz G, Paris M, Karmaus A, Strickland J, Allen D, Kleinstreuer N, Casey W. 2017. [Replacing animals for acute systemic toxicity testing: A U.S. strategy and roadmap](#) [poster]. Baltimore: Society of Toxicology 56<sup>th</sup> Annual Meeting and ToxExpo.

<sup>10</sup>Hamm J, Sullivan K, Clippinger AJ, Strickland J, Bell S, Bhatarai B, Blaauboer B, Casey W, Dorman D, Forsby A, *et al.* 2017. [Alternative approaches for identifying acute systemic toxicity: Moving from research to regulatory testing](#). *Toxicol In Vitro*. 41:245-259.

<sup>11</sup>Allen D, Wilson D, Hotchkiss J, Morefield S, Casey W, Clippinger A. 2017. [Integrating alternative approaches to replace animals in inhalation toxicity testing](#) [poster]. Seattle: 10<sup>th</sup> World Congress on Alternatives and Animal Use in the Life Sciences.