THE HUMANE SOCIETY
OF THE UNITED STATES



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**RE: ICCVAM Strategic Roadmap**

Dear Dr. Wolfe:

On behalf of The Humane Society of the United States (HSUS) and our members, we thank you for the opportunity to comment on the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) strategic roadmap. The HSUS and our international affiliate Humane Society International work in the United States and around the globe to encourage the development and implementation of non-animal test methods that represent the best available science while also preventing the suffering of millions of animals each year. We are grateful that ICCVAM has decided to evaluate its past process for new method assessment and to proactively engage agencies in the strategic planning.

ICCVAM's legislated mission is to "facilitate development, validation, and regulatory acceptance of new and revised regulatory test methods that reduce, refine, and replace the use of animals in testing while maintaining and promoting scientific quality and the protection of human health, animal health, and the environment."[1] However, as Dr. Casey recounts in the introduction to the September 11, 2017 Draft US Strategic Roadmap, "ICCVAM's evaluations of new methods followed a linear, stepwise validation model that proved to be lengthy, inefficient, and resource-intensive."[2] We fully support ICCVAM's stated goals for improving test development and implementation: (1) connecting end-users with the developers of NAMs; (2) fostering the use of efficient, flexible, and robust practices to establish confidence in new methods; and (3) encouraging the adoption and use of new methods and approaches by federal agencies and regulated industries.[3] With the aim of supporting and elaborating on recommendations in the draft roadmap, HSUS proposes the following short and longer term goals for each of these strategic goals. Although the draft roadmap is presented as consisting of two parts, a strategic and an implementation roadmap, we will address both aspects together under the headings of the former.

[1] National Toxicology Program (2017). ICCVAM Mission and Vision. Retrieved from https://ntp.niehs.nih.gov/pubhealth/evalatm/iccvam/mission-and-vision/index.html
[2] National Toxicology Program (2017). The U.S. Strategic Roadmap: New Approaches to Evaluate the Safety of Chemicals and Medical Products. Retrieved from https://ntp.niehs.nih.gov/iccvam/docs/about_docs/roadmapdraft-11sept.pdf
[3] *Ibid.*

***Strategic Goal: Connect End-users with the Development of New Tools***

Short Term Goals

As referenced in the draft strategic roadmap, there is a clear need for greater engagement of both federal agencies and industry at the beginning of new alternative method (NAM) development and throughout the evaluation and implementation process. Furthermore, this process would be greatly facilitated by the identification and engagement of key decision makers within each agency, in order to develop the relationships that are needed to drive successful implementation of NAMs. It is important that ICCVAM work both with experts and end-users of the methods to drive change from the ground up, while simultaneously securing support and directive from agency leaders who can drive investment and uptake. Ultimate success is likely going to depend on both top-down and bottom-up commitment from the agencies.

Another key activity to facilitate implementation is for ICCVAM to work with the agencies to develop transparent communication of their intent and acceptance of alternative methods. Some positive examples of leadership in this area come from Environmental Protection Agency (EPA)'s Office of Pesticide Programs (OPP), where in 2016 the then Director, Jack Housenger, issued a proclamation stating that "OPP's immediate goal is to significantly reduce the use of animals in acute effects testing…"[4] OPP has also articulated its "Strategic Vision for Adopting 21st Century Science Methodologies" on a webpage devoted to this topic.[5] ICCVAM could work with other offices, centers and agencies to develop similar visions, plans and webpages.

In addition, HSUS supports and encourages ICCVAM to immediately begin an initial scoping exercise where the priority activities and information needs of each agency are mapped. Such a mapping exercise will allow for the identification of areas of overlap between agencies and permits ICCVAM to determine where their strategic input would have the greatest impact, and thus on which methods they should focus validation efforts and resources. By getting a better understanding of the agencies' needs and priorities, ICCVAM can identify projects that will result in strong agency support. At the same time, this scoping exercise would allow ICCVAM to identify and suggest additional areas where improvements in NAMs would benefit agency obligations.

As mentioned in the draft roadmap, there is a need for greater communication among regulators, industry, and new method developers in order to continue productive dialogue on agency requirements and the path forward on new method development and application. HSUS agrees with ICCVAM's proposed plan to take a proactive role in setting up meetings, workshops, and webinars with all stakeholders. These efforts will be an important first step to prioritize ICCVAM projects and encourage collaboration like the FDA-Emulate partnership referenced below.

Longer term goals

ICCVAM could explore with the National Institutes of Health (NIH) the possibility of establishing grant review criteria tailored to the development and use of alternative methods. Currently, each Funding Opportunity Announcement (FOA) from the NIH will specify the review criteria and considerations that are to be used in evaluating those applications. Applications are awarded scores for each of five Scored Review Criteria (e.g. Innovation) and are also evaluated based on Additional Review Criteria[6], which are not scored individually but are taken account of in the overall impact score. For example, the use of vertebrate animals forms one of the

[4] Housenger, J. 2016. In a letter to stakeholders, available from the Federal Register, document number: EPA-HQ-OPP-2016-0093-0003.
[5] EPA (n.d.). Strategic Vision for Adopting 21st Century Science Methodologies. Retrieved from: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/strategic-vision-adopting-21st-century-science
[6] NIH (2016). Review Critera at a Glance. Retrieved from: https://grants.nih.gov/grants/peer/guidelines_general/Review_Criteria_at_a_glance.pdf

Additional Review Criteria. We suggest that developing an Additional Review Criterion that specifically considers the development and use of NAMs would be appropriate and timely and would help to promote consideration of these methods by the grant reviewers. Additionally, we envisage that a formal requirement to report on the applications of NAMs would help in determining trends in their use. Adding NAMs to the Additional Review Criteria should make it possible for ICCVAM, with the appropriate permissions of the NIH (since Grant Reviews are not public documents), to track the number of applications that propose the use of NAMs, and the number of successful applications employing new alternative methods. The inclusion of a review criterion that requires reporting of the use and development of NAMs could provide a valuable additional metric, of use in monitoring the uptake of NAMs.

The development and implementation of NAMs to satisfy agency needs and to develop better measures for improving human and environmental health will require a significant investment from the federal government as well as industry. ICCVAM is fortunate to be housed within one of the major institutes of the world's largest research funding body, the NIH, which has the capacity to impact the course of scientific research. ICCVAM might consider convening a task force with members from the Office of the Director, the National Center for Advancing Translational Sciences, and heads of disease-focused institutes on how to leverage new (and non-animal) technologies to better address disease research, and how ICCVAM could facilitate that process. Nearly five years ago, a previous director of NIH, Elias Zerhouni, said "We have moved away from studying human disease in humans…we all drank the Kool-Aid on that one, me included…The problem (of relying on animal models) is that it hasn't worked, and it's time we stopped dancing around the problem…we need to refocus and adapt new methodologies for use in humans to understand disease biology in humans."[7] More recently, the current director of NIH, Francis Collins, has stated in testimony before congress that "I predict that 10 years from now, safety testing for newly developed drugs, as well as assessment of the potential toxicity of numerous environmental exposures, will be largely carried out using human biochips that are loaded with cells accurately representing heart, liver, kidney, muscle, brain, and other tissues. This approach, made possible by the dramatic development of induced pluripotent stem cells (iPS cells) will mostly replace animal testing for drug toxicity and environmental sensing, giving results that are more accurate, at lower cost and with higher throughput."[8]

The NIH has the capability and capacity to make this happen and ICCVAM could play a critical facilitating role. Initially this could be achieved through special grant initiatives, for example, a recent Funding Opportunity Announcement from the NIH and NIEHS, requesting proposals from small business concerns to develop screening systems based on three dimensional or organotypic models.[9] This focused call for applications employing physiologically relevant *in vitro* systems represents an important advance. We feel that ICCVAM could encourage this further and that, with longer-term awareness and demonstration that the newer methods provide more human-relevant information, a commensurate shift should be reflected in NIH disease-related funding. This may happen naturally; however, ICCVAM could play a vital role by laying the groundwork for cost/benefit analyses of research, through many of the initiatives outlined already in this roadmap, such as setting up metrics and review of performance of animal tests. ICCVAM could consider including activities such as reviews of animal models, similar to those being funded through Humane Society International[10] or the reviews of non-animal methods for disease research from the European Centre for Validation of Alternative Methods.[11]

[7] https://nihrecord.nih.gov/newsletters/2013/06_21_2013/story1.htm
[8] https://blog.humanesociety.org/wayne/2016/06/congress-clears-landmark-bill-reduce-animal-use-chemical-testing.html
[9] NIH (2017). Organotypic Culture Models developed from Experimental Animals for Chemical Toxicity Screening (R43/R44) Retrieved from: https://grants.nih.gov/grants/guide/rfa-files/RFA-ES-17-008.html.
[10] Human Toxicology Project Consortium (n.d.). Publications from Funded Applications. Retrieved from: https://humantoxicologyproject.org/biomed-21-workshops/publications-from-funded-applications/
[11] EURL-ECCVAM (2017). Call for Tender - Review of non-animal methods used in disease research. Retrieved from: https://eurl-ecvam.jrc.ec.europa.eu/call-for-tender-review-of-non-animal-methods-used-in-disease-research

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

Short term goals

Establishing regulatory confidence in non-animal test methods often relies on comparison with *in vivo* data that has often proven to be less than effective at predicting human responses. The limitations of traditional animal tests and the data generated from these methods should be considered as part of the validation process for new alternative methods. Whenever possible, human data should be the benchmark against which new test methods are evaluated. We realize that human data for most types of chemicals and toxicities are not widely available, but where they are, ICCVAM could work with industry, particularly in the pharmaceutical and personal care product sectors, to figure out how they can make more of their historical human data available for this analysis. We agree that where human data is not available, ICCVAM should encourage the collection of parallel data from *in vivo* and *in vitro* studies; however, this should be seen as an interim and temporary measure until confidence in the NAM under consideration has been established.

In addition, prior to the initiation of any specific NAM assessment process, ICCVAM could enhance the chance of successful adoption by working with the relevant agencies to ensure that the appropriate chemicals are selected for evaluation that demonstrate the methods relevance and performance with respect to its intended use, including sufficiently broad chemical representation to ensure applicability to all relevant product sectors. Agencies are often reluctant to accept non-animal approaches because they were not validated to meet their specific needs. This, in turn, makes industry uneasy about pursuing these new test methods. A positive example of agency involvement is the Defense Advanced Research Projects Agency (DARPA) – NIH – Food and Drug Administration (FDA) partnership to develop organs-on-a-chip.[12] Both DARPA and FDA were involved from the beginning to ensure development of this new technology addressed their needs, and thus both agencies have a vested interest in the successful adoption. In April, FDA announced a partnership with Emulate, Inc., a company developing Organs-on-a-Chip technology. The Center for Food Safety and Applied Nutrition (CFSAN) will begin this multi-year partnership by evaluating the company's liver-on-a-chip.[13] In addition to agency participation in development and evaluation of approaches, whenever possible, ICCVAM should encourage these types of public-private partnerships.

Longer term goals

To prepare for an eventual move away from reliance on comparison to animal data, ICCVAM could work with stakeholders to develop a set of criteria against which to evaluate emerging non-animal methods. This could mirror the framework recently proposed by the Health and Environmental Sciences Institute (HESI) that examines performance characterization (information that should be accessible for any new test method), model predictive performance (method's ability to produce relevant risk assessments), and utilization (criteria for determining if method will correlate with regulatory needs).[14] Together, these criteria address the reliability of new non-animal methods, take account of how well the methods predict risk, and ultimately determine whether the method will generate data acceptable for regulatory purposes. This approach is similar to the performance-based test guideline concept developed through the Organization for Economic Cooperation and Development

[12] NIH (2012). NIH funds development of tissue chips to help predict drug safety. Retrieved from: https://www.nih.gov/news-events/news-releases/nih-funds-development-tissue-chips-help-predict-drug-safety
[13] Fitzpatrick, S (2017). 'Organs-on-Chips' Technology: FDA Testing Groundbreaking Science. Retrieved from: https://blogs.fda.gov/fdavoice/index.php/2017/04/organs-on-chips-technology-fda-testing-groundbreaking-science/
[14] HESI Framework for Intelligent Non-Animal Methods for Safety Assessment Workshop (2016). Retrieved from: http://hesiglobal.org/event/frameworks-workshop/

(OECD)[15] which facilities the evaluation of new NAMs, as long as they have a similar performance to already validated methods, but falls short of providing a completely independent approach to evaluating new methods.

ICCVAM has undertaken reviews of the reliability of animal data and proposes to do more. We strongly support this activity as it is critical for understanding the performance characteristics of data that regulators have been using and also to understand the standards of comparison for NAMs. In addition to performance, it is critical to continue to evaluate how well animal studies reflect human outcomes. Human relevance of animal data is often assumed, but where data exists for comparison, the actual relevance can be limited. A 2002 article compared results from rabbit and human skin testing for 65 chemical substances. It found that chemical irritation classification from the animal tests was not correct 45% of the time.[16] During a May 2017 ICCVAM public meeting, Nicole Kleinstreuer presented a comparison of human clinical data with results of mouse and guinea pig skin sensitization studies for 150 chemical substances. The LLNA correctly identified chemical hazard 72-82% of the time and potency 54-60%, while the Buehler test identified hazard ~72% and potency ~60% of the time.[17] Animal tests have also shown great variability making it more difficult to trust the results. For example, a 2016 literature review to analyze variability of uterotrophic studies found "of the 70 chemicals with at least two GL (Guideline like) studies, 18 (26%) had discordant outcomes and were classified as both active and inactive."[18] ICCVAM's continued recognition of concerns related to both the variability of animal data and reliability as compared with human data needs to be an integral part of NAM evaluation.

ICCVAM's participation in the OECD Adverse Outcome Pathway program would also be an investment in a longer-term move away from reliance on animal data for NAM evaluation. As more AOP networks are entered into the AOP Wiki, it will be increasingly possible to evaluate NAMs by consistency with the knowledgebase rather than prospective animal testing (acknowledging that AOPs are informed by animal data). As included information covers more biological space, an annotated and evaluated database such as the AOP wiki will increasingly serve as a valuable reference for evaluating NAMs.

As mentioned in the draft roadmap, ICCVAM could facilitate webinars or training on new methods so that not only are stakeholders informed about their availability and potential applications, but regulators will gain confidence in understanding the methods and the data they produce. We support the suggested development of case studies that show successful use of NAMs. An example is ICCVAM's role in convening an International Coordination on Alternative Test Methods (ICATM) workshop to evaluate the different IATA for skin sensitization. The purpose of this workshop was to understand the availability of current NAMs, identify regulatory requirements for skin sensitization in different regions and any obstacles to using NAMs to satisfy those regulatory needs, establish criteria for regulatory use, and provide recommendations for regulatory applications.[19] This type of review of current endpoints and the methods available to replace animals for each would be incredibly helpful for establishing confidence in new test methods and regulatory agencies from across the globe could better understand how current methods fit into their needs.

[15] e.g. OECD (2016), Test No. 455: Performance-Based Test Guideline for Stably Transfected Transactivation In Vitro Assays to Detect Estrogen Receptor Agonists and Antagonists, OECD Publishing, Paris.
[16] M.K. Robinson *et al*. "Non-Animal Testing Strategies for Assessment of the Skin Corrosion and Skin Irritation Potential of Ingredients and Finished Products," Food And Chemical Toxicology. 40 (2002): 573–592
[17] Kleinsteuer, NC (2017). Skin Sensitization Update [PowerPoint slides]. Retrieved from https://ntp.niehs.nih.gov/iccvam/meetings/iccvam-forum-2017/03b-kleinstreuer-skinsens-508.pdf.
[18] Kleinstreuer, NC *et al.* "A Curated Database of Rodent Uterotrophic Bioactivity." Environ Health Perspect. 2016 May;124(5):556-62.
[19] Kleinsteuer, NC (2017). Skin Sensitization Update [PowerPoint slides]. Retrieved from https://ntp.niehs.nih.gov/iccvam/meetings/iccvam-forum-2017/03b-kleinstreuer-skinsens-508.pdf.

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

Short term goals

Several non-animal test methods have been validated by ICCVAM, but are not yet fully implemented by regulatory agencies. One example of this is a consequence of EPA's failure to adopt the use of the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) for pesticides. Non-animal methods validated to identify GHS classifications require additional studies to in order to be used under EPA's classification criteria. This secondary process is expensive, time-consuming for industry, and largely unnecessary (since it does not affect the actual safety of the chemical, and rarely, if ever, changes the precautionary labeling associated with classification). In order to help facilitate a resolution to this problem, ICCVAM could collaborate with EPA and stakeholders to determine the variability of classification based on animal tests vs. non-animal tests and help with understanding the impact of switching to GHS.

In order to fulfil ICCVAM's mission, it is important that new methods quickly receive approval from regulatory authorities, but also that there is a method by which ICCVAM follows up to ensure the successful uptake of these methods. Ten years after the 1999 ICCVAM validation of Corrositex,[20] a replacement for skin corrosion tests on rabbits, Peta discovered that the Department of Transportation (DoT) was still receiving rabbit data for classification purposes. Through communication with DoT, the organization realized that the chemical applicability of Corrositex was limited.[21] They reached out to the developer of the skin model to urge improvement of its ability to distinguish between corrosivity classes. Through this work, the testing guideline was ultimately updated in 2016.[22] While the collection and use of metrics (as described below) should help alleviate similar concerns in the future, ICCVAM could have a leading role in following up with agencies after the validation of NAMs to ensure that the methods are being fully implemented.

To promote acceptance by the regulated industries requires confidence on the part of the industry that the data generated are acceptable and that animal test data are no longer required. We agree with the draft roadmap that ICCVAM should act as conduit between industry and the agencies to provide reassurance that the agencies will accept data from the non-animal alternative methods. This important information could be posted on the website where the different agency requirements are clearly spelled out – in terms of which data they will accept and for which purpose. Agencies should be encouraged to make their test requirements transparent, consider the extent to which current non-animal alternatives are applicable to their needs and, importantly, identify gaps that will inform longer term planning.

Once available, metrics on animal use and successful implementation of non-animal methods should also be included on the website. These metrics will help to demonstrate both the successful uptake of the alternatives and the related decrease in animal use. Metrics will also point to places where uptake is lacking, and that may need follow-up. As each agency and center collects different information, metrics may need to be tailored to each office/center in order to accurately ascertain successes and failures in the use and implementation of NAMs. For example, pesticide registration requires a known set of data, and EPA's OPP collects standard submissions from pesticide manufactures where test methods (whether animal or alternatives) could be clearly

[20] National Toxicology Program (1999). Corrositex: An *In Vitro* Test Method for Assessing Dermal Corrosivity Potential of Chemicals. Retrieved from: https://ntp.niehs.nih.gov/iccvam/docs/dermal_docs/corprrep.pdf
[21] http://www.mediapeta.com/peta/PDF/DOT_IG_complaint.pdf
[22] OECD (2016). Test No. 431: In Vitro Skin Corrosion: Human Skin Model Test. Retrieved from: http://www.oecd-ilibrary.org/environment/test-no-431-in-vitro-skin-corrosion-reconstructed-human-epidermis-rhe-test-method_9789264264618-en

identified as could the use any data bridging or waivers. In contrast, cosmetics companies are not required to register with FDA's CFSAN so there is a lack of information about the types of tests that are being done. In cases such as these, industry could be encouraged to volunteer information about the endpoints being assessed and any use of animals, alternative methods, or data waiving.

Longer term goals

In order to encourage the adoption of new approaches, it is important to address institutional inertia and actively reduce the reliance on, or acceptance of, outdated, animal-based approaches. Therefore, ICCVAM could work with agencies to identify any reference to specific test methods that exist in current federal law and agency regulations (this could be part of the scoping exercise mentioned above). As regulations and legislation are updated over the years, changes can be made that will allow evolution of the science used to support regulatory decisions. An example of this is the 2016 update to the Toxic Substances Control Act,[23] which included replacement of all mention of "data" with "information," was purposefully agnostic with respect to specific testing requirements, and also included a section on minimizing vertebrate animal testing. Inclusion of the requirement to minimize vertebrate testing is more than an ethical consideration; this requirement also drives the development and implementation of better scientific methods.

Another approach that facilitates the implementation of NAMs is the concept of integrated approaches to testing and assessment (IATA) as formally articulated by the OECD.[24] As mentioned above, ICCVAM, through ICATM has already facilitated a workshop with regulators from around the globe to review IATA for evaluating skin sensitization. Through ICATM, ICCVAM should continue to pursue the development of IATAs that allow various countries and agencies to choose evaluation methods that are appropriate for their individual needs.

We are so grateful for ICCVAM's leadership in developing this strategic roadmap. It is clear that there is a commitment to refining the validation process to ensure the agencies and industry are utilizing the best available science while also reducing the use of animals. Please feel free to contact us if you have any questions or need further information about these recommendations.

Sincerely,

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[23] Frank R. Lautenberg Chemical Safety for the 21st Century Act (2016). Retrieved from: https://www.epa.gov/sites/production/files/2016-06/documents/bills-114hr2576eah.pdf

[24] OECD (2016). Guidance Document No. 260: Guidance Document For The Use Of Adverse Outcome Pathways In Developing Integrated Approaches To Testing And Assessment (IATA). Retrieved from: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2016)67&doclanguage=en