AN INTERNATIONAL ORGANIZATION DEDICATED TO PROTECTING THE RIGHTS OF ALL ANIMALS

PETA

PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS

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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 25th Federal Register Notice by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). We appreciate and support ICCVAM's efforts to develop a strategic roadmap. The National Research Council's (NRC) 2007 report *Toxicity Testing in the 21st Century: A Vision and a Strategy* set the stage for using robust *in vitro* and *in silico* methods that are more efficient and predictive of human health outcomes, and this roadmap will help realize this vision. Thank you in advance for considering the suggestions below as ICCVAM develops the roadmap.

Use of Existing Resources

To improve the rate of new method uptake, ICCVAM agencies and NICEATM should continue to engage stakeholders, use and expand upon existing infrastructures and resources, and be transparent. For example, last year, NICEATM requested data and information on approaches used for evaluating acute systemic toxicity. Public notices such as these allow stakeholders to support the replacement of animal tests by sharing data; providing funding; developing methods; and/or organizing webinars, workshops, or training sessions when needed. The EPA's Office of Pesticide Programs (OPP) Acute Toxicity Stakeholder Group is another example of how entities can collaborate on a common goal. Regular meetings attended by EPA, NICEATM, industry, and NGOs provide a forum for exchanging ideas, identifying data needs and data sources, and reporting progress on OPP's efforts to transition to non-animal methods. The strategic roadmap should include a path to develop similar stakeholder groups within other ICCVAM member agencies.

Establish Confidence in New Approaches

The traditional validation process is costly and inefficient, and cannot keep pace with method development. Additionally, comparing data from non-animal tests to data from animal tests that were never validated for their relevance to humans is problematic. Studies show wide variability in data

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from animal tests and significant physiological differences between humans and other animals.[1,2,3,4] In its roadmap, ICCVAM should include steps to streamline a validation process that encourages the timely implementation and acceptance of human-predictive approaches for toxicity testing.

To ensure that a particular non-animal method will be accepted, 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 FDA Center for Devices and Radiological Health (CDRH) introduced the Medical Device Development Tool (MDDT) pilot 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 can be used without ambiguity. The strategic roadmap should include a plan to develop similar tools within additional ICCVAM agencies, and to publicize case studies of successful or unsuccessful use.

In addition, the roadmap should encourage regulatory agencies to actively solicit the submission of parallel data from companies when it exists. When *in vivo* testing is required, parallel *in vitro* testing helps build a database for validation and familiarizes reviewers with the non-animal methods. Forums should be established to discuss how to fast-track regulatory acceptance of methods that industry is already using to screen substances in-house.

An understanding of mechanisms of toxicity is vital for the development of new toxicity tests and strategies. Adverse outcome pathways (AOPs) are critical to the design of non-animal testing strategies. The roadmap should encourage stakeholders to dedicate more resources to AOP development.

Increased access to existing data, including negative results, helps to advance the validation of non-animal strategies. NICEATM's new resource, the Integrated Chemical Environment (ICE), will accelerate validation of new methods by providing access to existing curated data for tens of thousands of chemicals. OPP has worked with NICEATM to share the results of hundreds of acute toxicity 'six-pack' studies, and the roadmap should include instructions for how additional agencies and companies can contribute data to this resource.

U.S. Harmonization

Agencies must ensure that reviewers have the time and resources to learn how to interpret data from new methods. This can be facilitated by hands-on training 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. Additionally, the roadmap should encourage companies and regulatory agencies to establish an internal committee charged with coordinating

[1] Adriaens et al. Retrospective analysis of the Draize test for serious eye damage/eye irritation: importance of understanding the *in vivo* endpoints under UN GHS/EU CLP for the development and evaluation of *in vitro* test methods. *Arch Toxicol.* 2014;88(3):701-23.
[2] Luechtefeld et al. Analysis of Draize eye irritation testing and its prediction by mining publicly available 2008-2014 REACH data. *ALTEX.* 2016;33(2):123-134.
[3] Bartek et al. Skin permeability *in vivo*: comparison in rat, rabbit, pig, and man. *J. Invest. Dermatol*. 1972;58:114-123.
[4] Ennever and Lave. Implications of the lack of accuracy of the lifetime rodent bioassay for predicting human carcinogenicity. *Regul. Toxicol. Phar.* 2003;38:52-57.

mandatory training for all new employees who conduct, recommend, or review toxicology studies, and facilitating ongoing training opportunities.

We also recommend that regular inter-agency discussions be held to share ways in which successful programs at one agency can be applied at another; for example, OPP's stakeholder group or CDRH's MDDT tool.

Encourage the Use of Predictive Non-Animal Methods

The ICCVAM public forum, SACATM meeting, and presentations by ICCVAM members at scientific conferences have increased transparency and engagement, and ICCVAM member agencies should consider additional opportunities to communicate with stakeholders. For example, regular updates via blog posts, teleconferences, emails, web-based presentations, or Twitter would help ICCVAM agencies reach a larger audience with information about the acceptance of new methods, data sharing opportunities, and other efforts. OPP's webpage "Strategic Vision for Adopting 21st Century Science Methodologies" is a good example of a centralized website with information about OPP's goals, ongoing efforts, and related guidance documents. The roadmap should include a process to help ICCVAM agencies develop similar centralized repositories of information and to use various forms of communication to update stakeholders.

A major barrier to the implementation of alternatives to animal testing is the lack of a federal statute that specifically requires the use of alternatives to animal tests, when they exist. Such "last resort" language exists in the E.U. Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation[5] and the amended Toxic Substances Control Act.[6] At the very least, agencies must adopt clear language on the acceptance—and preference—for non-animal methods. Agencies should ensure that industry is aware of all available non-animal methods and strategies, and should offer incentives, such as expedited review, when non-animal approaches are used. Frequently, the status of regulatory acceptance of specific methods is unclear. As an example, we recently discovered that, although CDRH accepts results from the human skin patch test under certain conditions, not all of CDRH's reviewers were aware of this fact. It is essential that the roadmap call for clarity and transparency amongst regulatory agencies and that the agencies develop resources similar to the OPP webpage mentioned above to further this goal.

Review and Modify Existing Requirements

Reviewing arbitrary animal test hazard category cut-off values will help identify instances where regulatory agencies can modify their information requirements to reduce animal use. For example, in some cases, such as acute systemic toxicity testing, certain OPP hazard categories can be combined without affecting the protection of human health.

Second, ICCVAM agencies should review whether they are actually using the data that result from currently required animal tests. For example, the one-year chronic toxicity test in dogs traditionally required for pesticide registration has been eliminated in a number of countries, starting with the U.S. in 2007, after retrospective analyses showed results were rarely used for setting exposure

[5] European Commission. Regulation (EC) No 1907/2006.
[6] US EPA. The Frank R. Lautenberg Chemical Safety for the 21st Century Act. 2016. Available at: www.epa.gov/assessing-and-managing-chemicals-under-tsca/frank-r-lautenberg-chemical-safety-21st-century-act.

limits. Similarly, the EPA released guidance in 2016 for waiving *in vivo* acute dermal systemic toxicity testing of pesticide formulations after conducting a review which concluded that hazard classification is rarely driven by this endpoint.[7] For pesticide approvals, the mouse carcinogenicity study has provided little to no value, and further investigation into this area could yield data in favor of eliminating this study entirely. Additionally, acute systemic toxicity testing for medical device extracts in animals is often negative[8]; thus, CDRH should review why these data are required and whether the animal test may be avoided. The ICCVAM roadmap should prioritize retrospective reviews of the value of animal tests in protecting human health and the environment.

Third, it is critical that the roadmap encourage federal and state agencies to transition to the globally harmonized system (GHS) of classification and labelling. New *in vitro* Organisation for Economic Co-operation and Development (OECD) test guidelines are developed to align with GHS classification and labeling categories. This single change would immediately save animals and expedite the adoption of new methods.

Monitor Success

The development of predictive animal-free test methods does not necessarily translate into their adoption by industry and regulators. Currently, it is virtually impossible to track the success of non-animal approaches because there is no federal requirement to report the numbers of the vast majority of animals used in regulatory testing—mice, rats, birds, and cold-blooded animals—as is required in the United Kingdom and E.U.

To overcome specific hurdles, it is necessary to know which factors are impeding reductions in animal use, such as lack of awareness about available alternative methods or the absence of global regulatory acceptance of non-animal methods. For example, OPP accepts the use of an alternate testing framework for classifying the eye irritation potential of antimicrobial cleaning products. However, the PETA International Science Consortium and the Institute for In Vitro Sciences found that very few product submissions have used the alternate framework since its implementation.[9] Identifying that there is an issue is the first necessary step in addressing it.

To monitor the successful implementation of non-animal strategies, the roadmap should recommend a path to requiring the reporting of (1) the number of animals used in testing; (2) for what endpoints animals are used; and (3) the number of animal versus non-animal tests submitted to and accepted by regulatory agencies.

Workshops

The roadmap should capitalize on the various workshops that NICEATM and ICCVAM have organized by asking agencies to provide regular public updates on their response to workshop recommendations. For example, NICEATM, various ICCVAM member agencies, and the PETA

[7] U.S. EPA Office of Pesticide Programs. Guidance for waiving acute dermal toxicity tests for pesticide formulations and supporting retrospective analysis. November 9, 2016. Available at https://www.epa.gov/sites/production/files/2016-11/documents/acute-dermal-toxicity-pesticide-formulations_0.pdf.

[8] Hamm et al. Alternative approaches for identifying acute systemic toxicity: Moving from research to regulatory testing. *Toxicol In Vitro*. 2017:pii: S0887-2333(17)30004-8.

[9] Clippinger et al. Bridging the gap between regulatory acceptance and industry use of non-animal methods. *ALTEX*. 2016;33(4):453-458.

International Science Consortium have co-organized several workshops in the past two years on systemic toxicity testing. Workshop proceedings have been published and presented in public forums, and working groups have been formed to accomplish the workshop recommendations. Workshop co-sponsors are coordinating the working groups and monitoring progress on established milestones and timelines.

In contrast, recommendations put forth during international workshops on the use of alternative methods in the development and testing of biologics have great potential to reduce animal use, 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, it is still unclear if and how agencies are promoting, tracking, or otherwise fostering the implementation of those new policies. For instance, following the 2011 NICEATM—ICCVAM Workshop on Alternative Methods for Rabies Vaccine Testing, the USDA Center for Veterinary Biologics introduced a number of new policies to reduce animal use and refine *in vivo* challenge procedures.[10,11] Yet, to the best of our knowledge, there has been no assessment of the impact of these policies on the use of animals or the degree to which they have been implemented by industry. Considering the expert deliberation and consensus-building that led to previous workshop recommendations and implementation strategies, we encourage ICCVAM and NICEATM to assess progress—and the need for follow-up workshops or other activities—in the strategic roadmap.

International Harmonization

While this roadmap will understandably be U.S.-focused, it must consider the effects of international regulatory acceptance. A full transition to a new, human-based toxicity testing paradigm is dependent on global regulatory agencies' acceptance of these methods. A troubling example is the one-year chronic dog test for pesticide registration. Despite the U.S. and E.U. eliminating the test years ago, it was required in Canada until recently (and eliminated following PETA's intervention) and, to the best of our knowledge, is still required in Japan, South Korea, and Argentina. The need to update regulatory requirements should be identified by the agency and addressed in a timely manner without the need for NGO engagement.

ICCVAM should include steps in the roadmap to identify and address areas where there is a lack of international harmonization. Companies, regulators, and NGOs can work together to identify countries that still require animal tests which the U.S.—or another country—has eliminated and support international agencies in updating their requirements. In addition to webinars, workshops, and publications on these efforts, discussions within International Cooperation on Alternative Test Methods (ICATM) or at the OECD may be useful to share information about animal tests that have be replaced and to help overseas agencies follow suit. An example of a recent success was a 2016 ICATM workshop that evaluated the suitability of non-animal Defined Approaches to assess the skin sensitization of chemicals.

[10] U.S. Department of Agriculture Center for Veterinary Biologics. Notice 12-12, Use of humane endpoints and methods in animal testing of biological products. May 25, 2012. Available at https://www.aphis.usda.gov/animal_health/vet_biologics/publications/notice_12_12.pdf.

[11] U.S. Department of Agriculture Center for Veterinary Biologics. Notice 13-10, Changes to the rabies virus NIH potency test validity requirements. July 26, 2013. Available at https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/usda/cvbnotice13-10-508.pdf.

Ecotoxicity

In addition to human health effects testing, the above suggestions apply to the development and implementation of non-animal methods for ecotoxicity. Currently, alternative test methods for eco- and terrestrial toxicity are not widely available or implemented in the U.S. There is an urgent need for further development of non-animal methods as vast numbers of fish and birds are used in this type of testing. The roadmap should include specific strategies to foster the expansion of alternatives in this area of toxicity testing.

Summary

While our scientific understanding and technological abilities have been quickly advancing, changes in strategies to address toxicity testing and regulatory acceptance of new strategies have been frustratingly slow, particularly considering the millions of animal lives that are at stake. To drive the overdue transformation of "toxicity testing from a system based on whole-animal testing to one founded primarily on *in vitro* methods…,"[12] the roadmap must be specific, it must include timelines for the replacement of animal tests, and it must assign ownership of responsibilities.

PETA would like to thank Drs. Warren Casey, Nicole Kleinstreuer, David Allen, and Anna Lowit for spearheading efforts to replace animal use and for their work within ICCVAM. It is obvious that specific personnel within certain agencies are leading these efforts while other agencies are lagging far behind. We encourage ICCVAM to identify potential future leaders within less responsive agencies and foster their engagement within ICCVAM. ICCVAM representatives who do not have the time, resources, or interest to actively foster the acceptance of non-animal methods should step down so that a more appropriate person can be appointed.

We look forward to commenting on the draft roadmap and are happy to assist in any way we can to help replace and reduce animal use. Please feel free to contact me with any comments or questions.

Kind regards,

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[12] National Research Council. Toxicity testing in the 21st Century: a vision and a strategy. Committee on Toxicity Testing and Assessment of Environmental Agents. Washington, DC: National Academy Press. 2007.