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Dear Dr. Brownlow,

These comments are submitted on behalf of People for the Ethical Treatment of Animals (PETA) in response to the National Institutes of Health’s August 2, 2023 Federal Register Notice “Scientific Advisory Committee on Alternative Toxicological Methods; Notice of Public Meeting; Request for Public Input” (88 FR 50884).

Session Ia: 5 years into ICCVAM Strategic Roadmap: Full Replacement of the Acute Tox 6-pack

We commend the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) for their work to develop and implement reliable and relevant non-animal approaches for assessing acute toxicity. Given the ever-increasing availability of robust non-animal test methods for acute toxicity, we encourage ICCVAM member agencies to adopt policies clarifying the acceptance of these methods. For example, the use of in vitro reconstructed human tissue models for assessing skin irritation potential of device extracts has been extensively validated, is included in an International Organization for Standardization (ISO) standard, and is accepted by the European Union member states, Australia, Japan, and China.1,2,3,4 The U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health, however, has yet to integrate this approach into its own guidance on use of the ISO standard.5 As another example, the U.S. Environmental Protection Agency (EPA) has published on substantial progress to advance the use of non-animal approaches for health effects including systemic toxicity,6,7 dermal absorption,8,9 and eye irritation.10 Final steps need to be taken to formalize the EPA’s acceptance of these approaches as policy guidance.

Some ICCVAM member agencies keep lists of representative methods that the agency may consider to meet their data requirements.11,12 These lists can be useful to the regulated industry to understand what methods are often accepted and to clarify that additional methods will be considered; i.e., the list is not exhaustive of all methods that could be used, rather, it provides select, representative methods that the agency may consider. However, these lists can
become problematic if they are not regularly updated or if there is not a process for nominating methods to add to the list. For example, under TSCA Section 4(h)(2)(C), the EPA is directed to maintain and regularly update such a list. This list was published in June 2018 and updated in December 2019 and February 2021.\textsuperscript{13,14} To remain relevant five years after the publication of the initial list and more than two years since its last update, there is a need for a process for adding methods and an updated list (for example, one that includes the use of the GHS additivity equation and the in silico CATMOS model for systemic toxicity predictions).

Several years after the publication of ICCVAM’s strategic roadmap, as well as similar individual ICCVAM agency roadmaps,\textsuperscript{15,16,17,18,19} it would be useful to analyze metrics on submissions using animal and non-animal test methods to help evaluate the impact of the roadmaps and subsequent activities and programs. The European Union has increasingly recognized the value of transparency in animal use data.\textsuperscript{20} With a history of reporting animal numbers, species, and use of animals in Member States, the European Commission’s statistical report expanded the scope of animals and uses covered starting in 2015, e.g., the inclusion of all species of Cephalopods and the creation and maintenance of genetically altered animals.\textsuperscript{21} The European Commission notes, “To progress towards the ultimate goal of full replacement, it is crucial to understand where, how and why animals are still required to be used for scientific purposes.”\textsuperscript{22} ICCVAM member agencies should do the same, including reporting (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; and/or (4) the number of waivers granted versus the number of required studies.

As ICCVAM member agencies look beyond the acute toxicity six-pack, in addition to advancing new methods, they should consider revisiting where non-animal methods are ready and available for implementation but are not fully accepted by agencies or being used by industry. For example, the mouse bioassay (MBA) is commonly used to test for marine biotoxins in shellfish in order to fulfil FDA data needs. More specific and sensitive methods are available—and are required in some countries—but the MBA is still commonly used in the U.S. As another example, millions of animals are likely used to produce antibodies per year, and replacement technologies are well developed and available, yet there has not been a concentrated effort to implement the use of non-animal antibodies.

**Session Ib: 5 Years into ICCVAM Strategic Roadmap: Evolution of Validation**

We congratulate ICCVAM on the publication of its draft framework for transparently and consistently establishing scientific confidence in test methods. Its swift and transparent adoption by ICCVAM member agencies will allow for the uptake of reliable and relevant scientific tools that will best protect human health and the environment. Our comments on this framework have been submitted and are available \url{here}.\textsuperscript{23}

**Session II: The Role of NAMs in Improving Environmental Health Protection**

Non-animal methods provide the opportunity to address human population variability and susceptibility that tests on animals cannot. In vitro assays and microphysiological systems can be
developed to represent specific populations to assess human health susceptibility and outcomes, and in silico models allow us to conduct more comprehensive clinical trials. Similarly, to improve environmental health protection, resources should be directed towards data sharing and the use of 21st century in vitro and in silico approaches for the timely evaluation of chemicals of concern, such as PFAS.

Thank you for considering our comments.

Sincerely,

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