PhysiciansCommittee
for Responsible Medicine
PCRM.ORG
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May 21, 2021

Re: Physicians Committee for Responsible Medicine ICCVAM Public Forum 2021 Input

Submitted via ICCVAMquestions@niehs.nih.gov

Dear ICCVAM members:

The Physicians Committee for Responsible Medicine is an NGO supported by over 175,000 members working for efficient, effective, and ethical research and testing. We would like to congratulate NICEATM, ICCVAM, and agency staff for a productive year full of activities that are leading towards integration of new approaches that improve research and testing while saving animals. We appreciate the opportunity to provide annual written and oral input on NICEATM and ICCVAM-related activities.

- We have seen that setting bold goals committing to replacement of animal tests helps prioritize and direct effort and resources towards achieving such goals. We ask all ICCVAM members to work within your organizations to achieve top-down commitments to replacement and reduction of animal use, and we encourage all agencies to use a reduction of the numbers of animals used in tests as one metric of success.

- We encourage EPA to continue to implement its published New Approach Methods Workplan and TSCA–focused NAMs plan (*Alternative Test Methods and Strategies to Reduce Vertebrate Animal Testing*). Continued clear communication about the priority of reducing and replacing animal tests is needed to ensure continued progress. We also encourage EPA to publish its process for nominating NAMs to the agency for consideration for the List of Alternative Test Methods and Strategies (or New Approach Methodologies [NAMs]), and to request stakeholder input on that process, in order to ensure that relevant and reliable NAMs can be taken up and used by submitters and the agency in a timely manner.

- So much work is underway to advance and build confidence in the science and technology of new approaches. Consistent clear communication from agencies that new approaches are welcomed and encouraged is very important. To help build confidence that these approaches will be accepted by regulators, we ask regulatory agencies to conduct internal reviews of regulations, guidance, and other policies, and update or create written policies to reflect agency acceptance of nonanimal approaches.

- Acute toxicity testing is one area where NICEATM/ICCVAM has led efforts to demonstrate nonanimal approaches are as predictive or more predictive of human outcomes than animal studies. We ask the ICCVAM acute toxicity workgroup to coordinate a review of agency submissions on acute toxicity studies and determine how the organizations can encourage industry to avoid animal use for these endpoints by submitting nonanimal approaches, waivers, or other studies to fill acute toxicity data needs.

- PCRM appreciates CPSC's recent guidance on the evaluation of alternative test methods. CPSC's 2012 list of currently accepted alternative test methods urgently needs to be updated. For example, while the murine local lymph node assay is listed as an alternative method for evaluating sensitization, no mention is made of more recent defined approaches using *in vitro* and *in chemico* assays that have been shown to better predict results in humans. In addition, the guidance includes a lengthy discussion of formal validation frameworks. Historically, such frameworks have included comparisons to animal methods of questionable relevance and have presented barriers to the acceptance of alternatives. This has led to general recognition that these frameworks must be changed, and we urge CPSC to instead focus on the utility of the data produced by alternatives for its specific risk assessment needs.

- We are concerned by increasing use around the world of the term "applicability domain" to refer to the types of chemicals an *in vitro* method has been assessed with in validation datasets. This serves to restrict the recommended use of such methods to certain sectors, product types, or chemical classes without scientific basis, and is leading to larger and larger datasets and validation studies that need to be performed before a certain method can be used by specific agencies or for certain types of products. We encourage NICEATM and ICCVAM agencies to consider that there may not be any *a priori* reason that a particular chemical or mixture is out of the domain of applicability of an assay unless data or knowledge provide this information. Consideration and discussion should be given to science-based applicability domain characterizations that capture known incompatibility or accuracy issues (such as, for example, solubility). These can help agencies consider whether data generated with a particular assay are relevant for the chemicals and products under their purview without conducting multiple sector-specific validation studies. We also encourage test method developers to identify Agency needs, including the phys/chem characteristics of regulated chemicals, when considering generating validation data.

- One purpose of a public forum is for the public and stakeholders to engage on relevant agency activities. For future meetings, we ask the organizers to consider returning to an organizational structure that allows more "real time" public input by inviting public input after individual or grouped presentations, rather than at the end of the day. The ability to provide input in response to presentations helps ensure the feedback reaches the appropriate ICCVAM representative.

Finally, we continue to be impressed by NICEATM leadership, as well as ILS/NICEATM and agency staff that are working to advance nonanimal methods. We look forward to continued collaboration over the next year.

Respectfully,

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