

May 13, 2016

Dr. Warren Casey, Director
National Toxicology Program Interagency Center for the Evaluation of Alternative
Toxicological Methods (NICEATM)
P.O. Box 12233
Mail Drop K2-16
Research Triangle Park, NC 27709

Sent to Dr. Elizabeth Maull via email at maull@niehs.nih.gov

Dear Dr. Casey,

The Physicians Committee for Responsible Medicine appreciates this opportunity to comment on the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) related activities. This comment highlights several key NICEATM and ICCVAM achievements that advance science while reducing, refining and replacing animal testing, and offers suggestions for additional activities.

Skin and Eye Irritation Testing

At the public forum last year, we learned that the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA) does not require Draize data for skin or eye irritation testing.

In October 2015, CDER issued guidance stating that in vitro or ex vivo tests should be used in lieu of the in vivo rabbit ocular irritation test, commonly known as the Draize test, for dermal route of administration where a new formulation contains a substance that has not been evaluated for ocular irritation.

The Physicians Committee commends CDER for this effort to clearly communicate to stakeholders that Draize data are not required. As this guidance recommendation is limited in scope, we look forward to additional FDA communication with broader applicability.

Communication with stakeholders is key to increasing use of human-focused alternatives to animal tests. Therefore, we suggest that NICEATM and ICCVAM establish a process whereby ICCVAM agencies communicate with NICEATM when policy changes are made that will reduce, refine or replace the use of animals in

testing. NICEATM should then take the lead on communicating such changes to the broader stakeholder community.

International Council for Harmonisation

The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) provides a unique opportunity for advancing human-focused alternative tests. Consistent with the ICH's goal to minimize animal testing, it is working on multiple safety guidance documents that will reduce or replace animal testing.

As mentioned at the ICCVAM public forum last year, without international agreement regarding the use of alternative tests, animal tests are likely to continue in order to meet international regulations, even where ICCVAM agencies advance alternative methods. FDA should establish a process for communicating and collaborating with the ICH regarding NICEATM and ICCVAM related activities.

As an ICCVAM and ICH member, FDA should communicate ICCVAM related activities to the ICH and lead ICH to issue more guidance on alternative methods. At the very least, FDA should work to establish flexibility in ICH Guidance to allow for evolving science and technology.

Validation of Human-Focused Tests

As you know, many human-based alternative tests exist. Our experience working with technology developers suggests formal validation remains a hurdle to the increased use of human-focused alternatives to animal testing.

We commend NICEATM and ICCVAM on previous validation work and encourage continued assistance and funding opportunities, such as the National Institute of Environmental Health Sciences Small Business Innovation Research (NIEHS SBIR) grants, to help move alternatives forward. We support NICEATM's efforts to consider and implement new approaches for validating advancing technology by working with the Environmental Protection Agency (EPA) and the Organisation for Economic Co-operation and Development (OECD).

We are particularly concerned about the implementation of methods developed under the "Human on a Chip" partnership in which the Department of Defense (DOD), the National Institutes of Health (NIH), and FDA are funding and facilitating the development of microphysiological systems to evaluate potential disease treatments. There does not seem to be funding or planning in place for the integration of these methods into FDA's current regulatory framework. Given the amount of resources being invested in the project, we would like to encourage the FDA and the National Center for Advancing Translational Sciences (NCATS) to consider validation, training, and implementation activities in order to facilitate broader and faster use of any methods resulting from this groundbreaking project.

Developmental Toxicity

Developmental toxicity is an area where enormous scientific strides have been made and technologies exist that could potentially replace the use of large numbers of animals. We encourage NICEATM and ICCVAM to evaluate the field of alternatives for developmental toxicity screening to determine which modern technologies are ready for evaluation and regulatory uptake in place of some or all current in vivo requirements.

An Adverse Outcome Pathways approach is encouraged to assess assay development needs and the potential for existing assays to contribute to regulatory decision-making.^{1,2}

Endocrine Disruptor Screening Program

We support the direction EPA is moving to assess chemicals under the EDSP, and we are excited by the cooperation between NICEATM and EPA to make progress in developing a mixed in vitro/computational approach to assessing endocrine activity. We support a risk-based approach that takes potency and exposure into account when determining whether to conduct higher-tiered testing.

We are looking forward to seeing progress in assay development for chemical effects on thyroid pathways, and we encourage EPA to integrate pathway-based thinking into its consideration of testing needs for higher-tiered assessments, and reduce or tailor any Tier II data call ins as the program continues.

Finally, we appreciate the efforts EPA and NICEATM are making to educate other regulatory entities on its approach to endocrine assessment and to make its data and assays available to scientists and regulators in other regions. We suggest cooperation with other stakeholders, such as the Physicians Committee or ICAPO, to hold educational seminars or information-sharing workshops to assist with and expand upon these efforts. While EPA can, and is, leading by example, real progress in transitioning away from apical animal tests can only be accomplished with global buy-in.

National 3Rs Strategy

The Physicians Committee looks forward to discussing a national strategy to replace and reduce animal use at ICCVAM's advisory committee—the Scientific Advisory Committee on Alternative Toxicological Methods—later this fall. We share the commitment for a unified, high-level strategy accepted across the federal

¹ [Knapen D](#), [Vergauwen L](#), [Villeneuve DL](#), [Ankley GT](#). The potential of AOP networks for reproductive and developmental toxicity assay development, *Reprod Toxicol*. 2015 Aug 15;56:52-5. doi: 10.1016/j.reprotox.2015.04.003.

² International STakeholder NETwork (ISTNET): creating a developmental neurotoxicity (DNT) testing road map for regulatory purposes. [Bal-Price A](#), [Crofton KM](#), [Leist M](#), et al. *Arch Toxicol*. 2015 Feb;89(2):269-87. doi: 10.1007/s00204-015-1464-2.

government. At its core, this should be a replacement strategy, while not losing sight of reduction opportunities.

Training

The Physicians Committee recognizes that industry and regulator training is essential to increased use and acceptance of human-focused alternatives. We commend NICEATM and ICCVAM on their commitment to improving the workforce through education, such as webinars. We look forward to continued opportunities to collaborate on industry and agency training.

We would also like to request that in their next updates, ICCVAM member agencies outline what kinds of regular training opportunities are currently in place, or whether specific training opportunities have recently taken place or are planned, regarding in vitro or computational methods. We are particularly interested in training efforts directed towards the use and data interpretation of such methods by dossier reviewers, as these staff represent a “front line” in the acceptance of data from new methods.

6-Pack Waivers

The Physicians Committee commends the EPA on its March 2016 announcement that to better ensure protection of human health, its immediate goal was to significantly reduce the use of animals in acute testing requirements, collectively called the ‘6-pack’ of studies. We also applaud the EPA for issuing final guidance outlining a process to evaluate and implement alternative test methods, and for the release of a draft policy to waive the acute dermal toxicity tests for formulated pesticide products, and the initiation of several data analyses that will support the reduction or replacement of other 6-pack in vivo tests. The Physicians Committee looks forward to continued opportunities to support EPA’s efforts to replace these animal tests with new methods.

Dermal Absorption

Another opportunity for EPA to reduce animal testing involves the endpoint of dermal absorption (DA). An in vitro method for DA exists, using in vitro dermatomed skin. In fact, the assessment of DA via in vitro methods is an established practice in every sector except pesticides, and in vitro DA assessment is accepted in place of in vivo DA by European regulators. When in vivo and in vitro studies with comparable protocols are reviewed³, the in vitro method provides an appropriate assessment of the potential for pesticides to be dermally absorbed, which can be used for risk assessments.

We encourage the EPA and NICEATM to become involved in an ongoing effort with industry and NGO stakeholders to replace the rat dermal absorption method. One important feature of any such effort is a recognition that well-conducted in vitro

³ [Lehman PA1](#), [Raney SG](#), [Franz TJ](#). Percutaneous absorption in man: in vitro-in vivo correlation. *Skin Pharmacol Physiol*. 2011;24(4):224-30. doi: 10.1159/000324884.

studies using human skin are simply more relevant for protecting humans than in vivo rat studies.

The Physicians Committee is inspired by NICEATM and ICCVAM's work this year under Dr. Casey and Dr. Kleinstreuer's leadership. We look forward to continued progress and collaboration to improve science, reduce, refine and replace animal tests, and bring safer and more effective medicines to patients.

Warm regards,

Aryenish Birdie
Regulatory Testing Policy Specialist
abirdie@pcrm.org

Elizabeth Baker, Esq.
Senior Science Policy Specialist
ebaker@pcrm.org

Physicians Committee for Responsible Medicine
5100 Wisconsin Ave. NW Suite 400
Washington, D.C. 20016