

May 12, 2017

Dr. Warren Casey, Director
National Toxicology Program Interagency Center for the Evaluation of Alternative
Toxicological Methods (NICEATM)
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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 NICEATM and ICCVAM-related activities. We commend NICEATM and ICCVAM on key achievements and offer suggestions for additional activities.

Strategic Roadmap to Establish New Approaches for Evaluating the Safety of Chemicals and Medical Products in the United States

At the public forum last year, Dr. Casey described NICEATM's initial ideas for determining a specific strategy for modernizing the safety assessment of drugs and chemicals in the United States. We have been impressed with NICEATM's ability to coordinate consensus among ICCVAM agencies. NICEATM and ICCVAM's dedication to this initiative has been apparent throughout the year, including updates that were provided at the 2016 Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) meeting and the 2017 Society of Toxicology (SOT) Annual Meeting.

We were thrilled to learn that such a large number of participants from various ICCVAM agencies collaborated in person and via the web in February 2017 to identify a core strategy for the initiative that includes a cogent vision, mission and goals. The Physicians Committee supports the vision and mission, as outlined in the NICEATM federal register notice¹. We are confident that the initiative will lead to

¹ U.S. Department of Health and Human Services, National Toxicology Program, Strategic Roadmap to Establish New Approaches for Evaluating the Safety of Chemical and Medical Products in the United States, available at <https://ntp.niehs.nih.gov/pubhealth/evalatm/natl-strategy/index.html>, last visited May 3, 2017.

further development and use of physiologically relevant approaches that replace traditional animal tests that have been unable to provide the level of predictivity needed.

We appreciate NICEATM and ICCVAM's request for stakeholder input and involvement on tasks and objectives. As the national strategy and roadmap is intended to improve assessment of chemical and medical products, drugs and devices are included. We encourage NICEATM and ICCVAM to actively engage the preclinical pharmaceutical and stakeholder community in activities to ensure full representation. A strong emphasis on drug development is necessary; as it appears other sectors are more committed to accepting and implementing modern alternative approaches. Advances in preclinical drug testing will help regulators and industry make informed decisions earlier in the development process.

Making progress on this roadmap will require sustained participation and funding from all ICCVAM member agencies (and other stakeholders) to support the basic and regulatory science research needed to replace animal tests. Given this, we are deeply concerned by recent proposals to dramatically cut the Environmental Protection Agency (EPA) research budget. As part of the roadmap discussions, please consider discussion of potential solutions to this potential roadblock, including reorganizing other research funds from other ICCVAM member agencies towards the development of more human-relevant test methods.

We look forward to ongoing participation as the roadmap continues to develop.

Tissue/Organ Chips

At the forum last year, we heard updates from multiple agencies regarding tissue/organ chips. We have been impressed with progress made by the National Institutes of Health (NIH) on the Tissue Chips for Drug Screening program, led by the National Center for Advancing Translational Sciences (NCATS), and the Defense Advanced Research Projects Agency (DARPA) Microphysiological Systems program. We were pleased to learn about the Center for Food Safety and Applied Nutrition's (CFSAN) recent announcement to evaluate organ chips, and encourage the Center for Drug Evaluation and Research (CDER) to communicate its efforts to evaluate organ chips for drug safety assessment.

Skin Sensitization

From good work done by NICEATM and ICCVAM, we can say that several nonanimal approaches to skin sensitization provide comparable performance to the Local Lymph Node Assay (LLNA). We encourage the EPA to formalize this science into regulatory policy. First, we thank EPA for its work so far to support the work to propose and develop an OECD Test Guideline (TG) using alternative approaches, and we encourage EPA Office of Pesticide Programs (OPP) and the Office of Pollution Prevention and Toxics (OPPT) to participate in and expedite the OECD Test Guideline development process to ensure a harmonized test guideline is available for use as soon as possible. A final and necessary step in this process is to

delete the EPA and OECD *in vivo* test guidelines for skin sensitization as more advanced test methods and approaches become available and harmonized.

We also encourage EPA OPP and OPPT to issue interim guidance that *in vitro* data from well-performing Integrated Approaches to Testing and Assessment (IATA) (which could include well-established IATAs² or internal approaches that meet performance standards) for skin sensitization will be accepted in advance of the OECD TG publication.

Endocrine Disruptor Screening Program (EDSP)

Another area of recent success is the progress NICEATM and EPA have made with EDSP²¹. The performance of the Estrogen Receptor (ER) pathway model can replace the uterotrophic assay and provides better mechanistic coverage. The Androgen Receptor pathway model has the potential to do the same. However, we have been concerned by lack of progress on the implementation of these models into the EDSP and the OECD. Endocrine Disruption is an issue of global interest and importance, and it is incumbent on EPA to harmonize valid and useful approaches to assess the endocrine-disrupting potential of chemicals with other governments, especially if these approaches can replace the *in vivo* test guidelines it helped to establish at the OECD.

Cognizant of the time that may be required to adopt performance-based test guidelines modeled on the ER or AR pathway model at the OECD, we recommend EPA create its own performance-based test guidelines to replace its own uterotrophic and Hershberger test guidelines, and propose projects at the OECD level to do the same without delay.

Conclusion

The Physicians Committee continues to be impressed by NICEATM and ICCVAM's leadership in modernizing safety assessment. Some agencies have sought creative solutions to replace animal test requirements and, together with NICEATM, made enormous progress. We look forward to this progress inspiring all ICCVAM representatives to drive continued progress and collaboration within their agencies to improve science, reduce and replace animal tests, and better protect humans.

² No. 256 Guidance Document on the Reporting of Defined Approaches and Individual Information Sources to be Used Within Integrated Approaches to Testing and Assessment (IATA) for Skin Sensitisation:

[http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2016\)29&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2016)29&doclanguage=en), Annex 1:

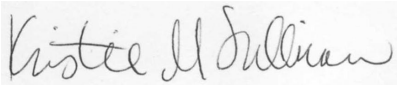
[http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2016\)29/ann1&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2016)29/ann1&doclanguage=en), Annex 2:

[http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2016\)29/ann2&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2016)29/ann2&doclanguage=en)

Respectfully submitted,



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