

Update on the March 29-30, 2011, NICEATM-ICCVAM Independent Scientific Peer Review Panel Evaluation of an *In Vitro* Estrogen Receptor Transcriptional Activation Assay for Endocrine Disruptor Chemical Screening

The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) convened an international independent scientific peer review panel on March 29-30, 2011 on behalf of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). The Panel met at the William H. Natcher Conference Center on the main campus of the National Institutes of Health in Bethesda, Maryland to evaluate the validation status of the LUMI-CELL[®] test method, according to established Federal and international criteria.¹ Dr. John Vandenberg of North Carolina State University chaired the public meeting of the Panel, composed of 16 independent scientists from the U.S., Japan, Canada, South Korea, Italy, and Germany.

Studies have indicated that animal populations exposed to high levels of estrogen active substances have an increased incidence of reproductive and developmental abnormalities. These findings have raised concerns about the potential public health and environmental effects of these substances. Accordingly, the Environmental Protection Agency initiated the Endocrine Disruptor Screening Program (EDSP) to develop a multi-test strategy to screen pesticides and environmental contaminants for their potential to affect the endocrine systems of humans and wildlife.

The LUMI-CELL test method measures transactivation of an estrogen responsive luciferase reporter gene in human ovarian cancer cells to assess substances for *in vitro* estrogen agonist and antagonist activity. This test could be used as one component of the multi-test screening strategy described in the EDSP and offers potential benefits over the existing method. LUMI-CELL is the only transactivation assay validated for assessing *in vitro* estrogenic activity up to the 1 mM limit currently required in the EDSP, and is also the only method to be validated for the detection of anti-estrogenic substances.

Draft Peer Review Panel Conclusions

The summary presented here should be considered preliminary or draft pending the publication of the Panel's final report, which will be published in May 2011.

The Panel considered the results of an international interlaboratory validation study that included laboratories in the United States, Italy, and Japan. Based on their evaluation of these data, the Panel reached the following conclusions:

1. The Panel agreed with ICCVAM's draft test method recommendation that the LUMI-CELL method can be used as a screening test to identify substances with *in vitro* estrogenic and anti-estrogenic agonist activity.

¹ ICCVAM validation and acceptance criteria are provided in the document, *Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods*, available at http://iccvam.niehs.nih.gov/docs/about_docs/validate.pdf.

2. The Panel noted several advantages provided by this assay over the currently accepted test method for this endpoint, including the robust LUMI-CELL test method protocol, the validated testing range (up to 1 mM), and the ability to detect substances with *in vitro* anti-estrogenic activity.
3. The Panel endorsed the draft ICCVAM recommended test method protocols, and suggested future studies that should be conducted with these protocols to expand the usefulness of the LUMI-CELL test method
4. The Panel concurred with the draft ICCVAM performance standards that could be used to evaluate the validation status of test methods that are functionally and mechanistically similar to the LUMI-CELL test method

Next Steps

The Panel's final report, including its conclusions and recommendations, will be published in May 2011. It will be available on the NICEATM-ICCVAM website at <http://iccvam.niehs.nih.gov/methods/endocrine/PeerPanel11.htm>

Information considered by the Panel during the meeting is also available on this page. Dr. Vandenberg will also present a summary of the Panel's conclusions and recommendations at the upcoming public meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) at their public meeting on June 16-17, 2011, in Arlington, Virginia.

ICCVAM will consider the Panel's report along with all public and SACATM comments and prepare final test method recommendations that it will forward to Federal agencies as part of a comprehensive test method evaluation report. Prior to requiring, recommending, or encouraging the application of any new or revised toxicity test method, agencies must determine that the method is valid for its proposed use and that the method will provide for equivalent or improved protection of human health. The Panel's report and ICCVAM's evaluation will aid agencies in making these determinations. Agencies are required to respond to ICCVAM recommendations within 180 days.

Background on ICCVAM-NICEATM

ICCVAM is an interagency committee composed of representatives from 15 Federal regulatory and research agencies that require, use, generate, or disseminate toxicological and safety testing information. ICCVAM conducts technical evaluations of new, revised, and alternative safety testing methods with regulatory applicability and promotes the scientific validation and regulatory acceptance of toxicological and safety testing methods that more accurately assess the safety and hazards of chemicals and products and that reduce, refine (decrease or eliminate pain and distress), or replace animal use. The ICCVAM Authorization Act of 2000 established ICCVAM as a permanent interagency committee of the NIEHS under NICEATM (42 U.S.C. 285I-3). NICEATM administers ICCVAM, provides scientific and operational support for ICCVAM-related activities, and conducts independent validation studies to assess the usefulness and limitations of new, revised, and alternative test methods and strategies. NICEATM and ICCVAM work collaboratively to evaluate new and improved test methods and strategies

applicable to the needs of U.S. Federal agencies. Additional information about ICCVAM and NICEATM can be found on the NICEATM-ICCVAM Web site (<http://iccvam.niehs.nih.gov>).

Questions about the peer review evaluation of the BG1Luc ER TA test method or NICEATM can be directed to Dr. Warren Casey, the NICEATM Deputy Director, at 919-316-4729 or warren.casey@nih.gov.