DEPARTMENT OF HEALTH AND HUMAN SERVICES

Independent Scientific Peer Review Panel Report: Evaluation of the Validation Status of an In Vitro Estrogen Receptor Transcriptional Activation Test Method for Endocrine Disruptor Chemical Screening: Notice of Availability and Request for Public Comments

AGENCY: Division of the National Toxicology Program (DNTP), National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH).

ACTION: Notice of availability and request for comments.

SUMMARY: The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), on behalf of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), convened an independent international scientific peer review panel (hereafter, Panel) on March 29–30, 2011, to evaluate the validation status of the LUMI–CELL® (BG1Luc ER TA) test method, an *in vitro* transcriptional activation (TA) assay used to identify chemicals that can interact with human estrogen receptors (ERs). The Panel report is now available on the NICEATM–ICCVAM Web site at: *http://iccvam.niehs.nih.gov/docs/endo_docs/EDPRPRept2011.pdf* or by contacting NICEATM (see **ADDRESSES**). The report contains (1) the Panel's evaluation of the validation status of the test method and (2) the Panel's comments on the draft ICCVAM test method recommendations. NICEATM invites public comment on the Panel report.

DATES: Written comments on the Panel report should be received by July 5, 2011.

ADDRESSES: NICEATM prefers that comments be submitted electronically by e-mail to *niceatm@niehs.nih.gov.* Comments can also be submitted via the NICEATM–ICCVAM Web site at *http://iccvam.niehs.nih.gov/contact/FR_pubcomment.htm.* Written comments can be sent by mail or fax to Dr. Warren Casey, Deputy Director, NICEATM, NIEHS, P.O. Box 12233, Mail Stop: K2–16, Research Triangle Park, NC 27709; (fax) 919–541–0947. Courier address: NIEHS, NICEATM, 530 Davis Drive, Room 2035, Durham, NC 27713.

FOR FURTHER INFORMATION CONTACT: Dr. Warren Casey: (telephone) 919–316–4729, (fax) 919–541–0947, (e-mail) *niceatm@niehs.nih.gov.*

SUPPLEMENTARY INFORMATION:

Background

In January 2011, NICEATM announced the convening of an independent scientific peer review panel to review and comment on the draft background review document (BRD) summarizing available data, reliability and accuracy of the BG1Luc ER TA test method, the draft recommendations, as well as the availability of the draft documents for public comment (76 FR 4113). The Panel met in public session on March 29–30, 2011, at the Natcher Conference Center in Bethesda, MD. The Panel reviewed the draft ICCVAM BRD for completeness, errors, and omissions of any existing relevant data or information. The Panel also evaluated the information in the draft documents to determine the extent to which each of the applicable criteria for validation and acceptance of toxicological test methods (ICCVAM, 2003a) had been appropriately addressed. The Panel then considered the ICCVAM draft recommendations and commented on the extent that the recommendations were supported by the information provided in the draft BRD.

In January 2004, Xenobiotic Detection Systems, Inc. (XDS, Durham, NC) nominated their LUMI–CELL® BG1Luc ER TA test method for an interlaboratory validation study. This method uses BG–1 cells, a human ovarian carcinoma cell line that is stably transfected with an estrogen-responsive luciferase reporter gene to measure whether and to what extent a substance induces or inhibits TA activity via ER mediated pathways (Denison and Heath-Pagliuso, 1998). Included in the nomination package were test results from XDS for 56 of the 78 ICCVAM reference substances for agonist activity and 16 of the 78 ICCVAM reference substances for antagonist activity. These studies were funded primarily by an NIEHS Small Business Innovation Research (SBIR) grant (SBIR43ES010533–01).

In accordance with the ICCVAM nomination process, NICEATM conducted a preliminary evaluation of the nomination package to determine the extent to which it addressed the ICCVAM prioritization criteria and adherence to the ICCVAM recommendations for the standardization and validation of *in vitro* endocrine disruptor test methods (ICCVAM, 2003b). ICCVAM and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) recommended that the BG1Luc ER TA test method should be

considered a high priority for interlaboratory studies based upon the lack of adequately validated test methods and the regulatory and public health need for such test methods. Based on this evaluation, ICCVAM recommended that:

- The BG1Luc ER TA test method should be considered a high priority for interlaboratory validation studies as an *in vitro* test method for the detection of test substances with ER agonist and antagonist activity.
- Validation studies should include coordination and collaboration with the European Centre for the Validation of Alternative Methods (ECVAM) and the Japanese Center for the Validation of Alternative Methods (JaCVAM) and include one laboratory in each of the three respective geographic regions (United States, Europe, and Japan).
- In preparation for the interlaboratory validation study, XDS should conduct protocol standardization studies with an emphasis on filling data gaps in the antagonist protocol for the BG1Luc ER TA.

The NIEHS subsequently agreed to support the validation study in light of its role as one of the three NTP agencies, whose mission includes the development and validation of improved testing methods. Based on the results of this study, ICCVAM is now reviewing the validation status of this test method for identification of substances with *in vitro* ER agonist or antagonist activity. NICEATM and the ICCVAM Interagency Endocrine Disruptors Working Group prepared a draft BRD that provides a comprehensive description and the data from the validation study used to assess the accuracy and reliability of the BG1Luc ER TA test method. ICCVAM also developed draft recommendations for its use.

Availability of the Peer Panel Report

The Panel's conclusions and recommendations are detailed in the *Independent Scientific Peer Review Panel Report: Evaluation of the Validation Status of the BG1Luc4E2 ER TA (LUMICELL), an In Vitro Transcriptional Activation Assay Used to Identify Chemicals That Can Interact with Human Estrogen Receptors* which is available along with the draft documents reviewed by the Panel and the draft ICCVAM test method recommendations at *http://iccvam.niehs.nih.gov/methods/endocrine/PeerPanel11.htm.*

Request for Public Comments

NICEATM invites the submission of written comments on the Panel report. When submitting written comments, please refer to this **Federal Register** notice and include appropriate contact information (name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization, if applicable). All comments received will be made publicly available via the NICEATM–ICCVAM Web site at *http://iccvam.niehs.nih.gov/methods/endocrine/PeerPanel11.htm.* ICCVAM will consider the Panel report along with public comments and comments made by SACATM at their June 16–17, 2011 meeting (67 FR 23323) when finalizing test method recommendations. Final ICCVAM recommendations will be published in an ICCVAM test method evaluation report, which will be forwarded to relevant Federal agencies for their consideration. The evaluation report will also be available to the public on the NICEATM–ICCVAM Web site at *http://iccvam.niehs.nih.gov/methods/endocrine/ERTA–TMER.htm* and by request from NICEATM (see **ADDRESSES** above).

Background Information on ICCVAM, NICEATM, and SACATM

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 test methods that more accurately assess the safety and hazards of chemicals and products and that refine (decrease or eliminate pain and distress), reduce, and replace animal use. The ICCVAM Authorization Act of 2000 (42 U.S.C. 285l–3) established ICCVAM as a permanent interagency committee of the NIEHS under NICEATM. NICEATM administers ICCVAM and 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 welcome the public nomination of new, revised, and alternative 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).*

SACATM was established in response to the ICCVAM Authorization Act [Section 285l-3(d)] and is composed of scientists from the public and private sectors. SACATM advises ICCVAM, NICEATM, and the Director of the NIEHS and NTP regarding statutorily mandated duties of ICCVAM and activities of NICEATM. SACATM provides advice on priorities and activities related to the development, validation, scientific review, regulatory acceptance, implementation, and national and international harmonization of new, revised, and alternative toxicological test methods. Additional information about SACATM, including the charter, roster, and records of past meetings, can be found at *http://ntp.niehs.nih.gov/go/167.*

References

Denison MS, Heath-Pagliuso S. 1998. The Ah receptor: A regulator of the biochemical and toxicological actions of structurally diverse chemicals. Bull Environ Contam Toxicol 61(5): 557–568.

ICCVAM. 2003a. ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods. NIH Publication No. 03–4508. Research Triangle Park, NC.

ICCVAM. 2003b. ICCVAM Evaluation of In Vitro Test Methods For Detecting Potential Endocrine Disruptors: Estrogen Receptor and Androgen Receptor Binding and Transcriptional Activation Assays.

Dated: May 11, 2011.

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[FR Doc. 2011–12264 Filed 5–17–11; 8:45 am]

BILLING CODE 4140–01–P