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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Availability of ICCVAM Evaluation Report and Recommendations on the Usefulness and Limitations of the LUMI-CELL[®] ER (BG1Luc ER TA) Test Method, An *In Vitro* Assay for Identifying Human Estrogen Receptor Agonist and Antagonist Activity of Chemicals

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

ACTION: Availability of Report and Recommendations; Notice of Transmittal

SUMMARY: The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) announces availability of an Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) test method evaluation report (TMER) that includes recommendations on the usefulness and limitations of the LUMI-CELL[®] estrogen receptor (ER) transcriptional activation (TA) test method (hereafter referred to as the BG1Luc ER TA test method) to identify human ER agonist and antagonist activity of chemicals. The report also provides (1) performance standards that can be used to evaluate functionally and mechanistically similar test methods, (2) recommended test method protocols, (3) a final background review document (BRD) describing the current validation status of this test method, and (4) recommendations for future studies.

ICCVAM recommends that the BG1Luc ER TA test method can be used as a screening test to identify substances with *in vitro* estrogen agonist and antagonist activity. This use is based on an

evaluation of results from an international validation study and corresponding accuracy and reliability.

The report and recommendations have been transmitted to Federal agencies to review and respond to ICCVAM in accordance with the provisions of the ICCVAM Authorization Act of 2000 (42 U.S.C. 285I-2).

FOR FURTHER INFORMATION CONTACT: Dr. William S. Stokes, Director, NICEATM, NIEHS, P.O. Box 12233, Mail Stop: K2-16, Research Triangle Park, NC, 27709, (telephone) 919-541-2384, (fax) 919-541-0947, (email) niceatm@niehs.nih.gov. Courier address: NICEATM, NIEHS, Room 2034, 530 Davis Drive, Morrisville, NC 27560.

SUPPLEMENTARY INFORMATION:

Background

In January 2004, Xenobiotic Detection Systems, Inc. (XDS, Durham, NC) nominated the BG1Luc ER TA test method for an interlaboratory validation study. ICCVAM and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) recommended a high priority for the nominated study, based on the lack of adequately validated test methods and the regulatory and public health need for such test methods. NICEATM subsequently led and coordinated an international validation study with its counterparts in Japan (Japanese Center for the Validation of Alternative Methods) and Europe (European Centre for the Validation of Alternative Methods) in laboratories sponsored by each validation organization. ICCVAM also proposed the development of BG1Luc ER TA test method performance standards. ICCVAM assigned the activities a high priority after considering comments from the public and endorsement from SACATM.

ICCVAM established an interagency Endocrine Disruptor Working Group (EDWG) composed of scientists from the 15 Federal agencies represented on ICCVAM to work with NICEATM to carry out the relevant evaluation activities. Following completion of the validation study, NICEATM, ICCVAM, and the EDWG prepared a draft BRD and draft test method recommendations. NICEATM released the ICCVAM draft documents to the public for comment and convened an international independent scientific peer review panel (hereafter referred to as the Panel) in public session on March 29-30, 2011, to provide their conclusions on the draft BRD and draft ICCVAM test method recommendations (76 FR 4113). Stakeholders from the public were provided opportunities to comment throughout the review process, including the opportunity for oral comments at the Panel meeting. The Panel considered these comments, as well as public comments submitted prior to the meeting, before concluding its deliberations. The Panel report was published and made available to the public for review and comment (76 FR 28781). The draft test method recommendations, the draft BRD, the draft Panel report, and all public comments were made available to SACATM, which provided comments at its public meeting on June 16-17, 2011 (76 FR 23323).

ICCVAM considered the peer review panel report and all public and SACATM comments in preparing the ICCVAM final test method recommendations. Detailed ICCVAM recommendations are provided in the ICCVAM TMER, *The LUMI-CELL[®] ER (BG1Luc ER TA) Test Method: An In Vitro Assay for Identifying Human Estrogen Receptor Agonist and Antagonist Activity of Chemicals* (NIH Publication No. 11-7850, available at <http://iccvam.niehs.nih.gov/methods/endocrine/ERTA-TMER.htm>). ICCVAM recommends that the BG1Luc ER TA test method can be used as a screening test to identify substances with *in vitro* estrogen agonist activity. This use is based on an evaluation of available validation study

data and corresponding accuracy and reliability. ICCVAM recommends that the accuracy of this assay is at least equivalent to the current ER TA assay included in regulatory testing guidance. The ICCVAM TMER also includes the updated ICCVAM-recommended BG1Luc ER TA test method protocol, performance standards that are applicable to functionally and mechanistically similar test methods, the final BRD, relevant endocrine disruptor testing regulations and testing guidelines, applicable **Federal Register** notices, the Panel report, public comments, and SACATM meeting minutes.

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 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 (42 U.S.C. 2851-3) established ICCVAM as a permanent interagency committee of the NIEHS under NICEATM. 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 welcome the public nomination of new, revised, and alternative test methods and strategies applicable to the needs of Federal agencies. Additional information about NICEATM and ICCVAM can be found on the NICEATM-ICCVAM website (<http://iccvam.niehs.nih.gov>).

SACATM was established in response to the ICCVAM Authorization Act (Section 285/-3[d]) and is composed of scientists from the public and private sectors (67 FR 11358).

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>.

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