DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Toxicology Program (NTP), NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Notice of Availability of the NICEATM Pre-Screen Evaluation of a Cell Proliferation Assay To Detect Estrogenic Activity: Request for Comments and Nominations of Other In Vitro Endocrine Disruptor Test Methods

AGENCY: National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH), HHS.

ACTION: Report availability and request for comments and nominations.

SUMMARY: In January 2006, the Interagency Coordinating Committee on Alternative Methods (ICCVAM) received a test method nomination for the validation of a cell-based estrogen receptor (ER) transcriptional activation (TA) test method from CertiChem, Inc. CertiChem, Inc. submitted a background review document (BRD) containing information on historical development of the test method, the rationale for the test method, and supporting materials. In accordance with the ICCVAM nomination process, NICEATM conducted a pre-screen evaluation of the BRD to determine the extent that it addressed ICCVAM prioritization criteria, submission guidelines, and recommendations for standardization and validation of *in vitro* endocrine disruptor test methods. NICEATM also reviewed the performance of the test method based on pre-validation data to determine if it warranted consideration for further validation. ICCVAM requests public comments on the pre-screen evaluation titled, ''Pre-Screen Evaluation of the CertiChem, Inc. *In Vitro* Endocrine Disruptor Assay (Robotic MCF–7 Cell Proliferation Assay of Estrogenic Activity.)'' The pre-screen evaluation is available with supporting documents at (*http://iccvam.niehs.nih.gov/methods/endocrine.htm*). ICCVAM also invites public comments on whether this test method should be considered for additional validation studies. In addition, ICCVAM again invites the nomination of other *in vitro* ER and androgen receptor (AR) binding and TA test methods for which there are standardized test method protocols, pre-validation data, and proposed validation study designs.

DATES: Comments and nominations should be received by November 30, 2006.

ADDRESSES: Correspondence should be sent by mail, fax, or e-mail to Dr. William S. Stokes, NICEATM Director, NIEHS, P.O. Box 12233, MD EC–17, Research Triangle Park, NC 27709, (phone) 919–541–2384, (fax) 919–541–0947, (e-mail) *niceatm@niehs.nih.gov.*

SUPPLEMENTARY INFORMATION:

Background

In May 2003, ICCVAM published the report, ''ICCVAM Evaluation of *In Vitro* Test Methods for Detecting Potential Endocrine Disruptors: Estrogen Receptor and Androgen Receptor Binding and Transcriptional Activation Assays (NIH Publication No. 03–4503; available: *http://iccvam.niehs.nih.gov/methods/endocrine.htm*). The report recommends minimum procedural standards that should be incorporated in standardized test method protocols and minimum lists of chemicals that should be used for validation studies. A request was made for nominations of validation studies for *in vitro* ER and AR binding and TA test methods based on these recommendations and for which there are standardized test method protocols, pre-validation data, and proposed validation study designs (69 FR 21564). ICCVAM subsequently received a nomination from CertiChem, Inc. for the validation of a cell-based ER TA method that evaluates the estrogenic activity of substances by measuring whether and to what extent a substance induces cell proliferation via ER-dependent pathways. In support of this nomination, ICCVAM received a BRD containing information on the test method's historical development, its rationale, its protocol, and other supporting materials. In accordance with the ICCVAM nomination process, NICEATM conducted a pre-screen evaluation of the BRD to determine the extent that it addressed ICCVAM prioritization criteria, submission guidelines, and recommendations for standardization and validation of *in vitro* endocrine disruptor test methods. NICEATM also reviewed the performance of the proposed test method based on pre-validation data to determine if it warranted consideration for further validation. The BRD was reviewed for completeness and to identify aspects or omissions that could impede further review. The criteria considered in evaluating information provided in the BRD are:

- The extent to which the BRD addresses ICCVAM prioritization criteria.
- The extent to which the BRD provides the information requested in the *ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods* (NIH Pub. No. 03–4508, available at *http://iccvam.niehs.nih.gov*).
- The extent to which the proposed test method adheres to the recommendations of the *ICCVAM Evaluation of In Vitro Test Methods for Detecting Potential Endocrine Disruptors* (NIH Pub. No. 03–4503, available at *http://iccvam.niehs.nih.gov/methods/endocrine.htm*), especially those regarding essential test method components and recommended validation substances.
- The extent to which the proposed test method shows adequate performance (reliability and accuracy) during pre-validation to warrant consideration for validation studies.

Based on the pre-screen evaluation, ICCVAM made a draft recommendation that this test method be considered as a high priority for validation studies to

evaluate its usefulness and limitations for detecting substances with *in vitro* estrogenic agonist and antagonist activity, and that standardization of an anti-estrogenic protocol be developed prior to starting the main validation effort. ICCVAM will finalize its recommendations on the priority for future validation of this test method after considering comments received from the public and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) at their November 30, 2006 meeting.

ICCVAM also takes this opportunity to again invite the nomination of other *in vitro* ER and AR binding and TA test methods for which there are standardized test method protocols, pre-validation data, and proposed validation study designs (see also 69 FR 21564).

When submitting written comments and nominations 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 by the deadline listed above will be placed on the ICCVAM/NICEATM Web site and made available to ICCVAM. In addition, there will be an opportunity for oral public comments on the draft ICCVAM pre-screen evaluation during a meeting of the SACATM scheduled for November 30, 2006. Details of the SACATM meeting are published as a separate **Federal Register** notice (see *http://ntp.niehs.nih.gov/go/frn* for the **Federal Register** notice citation).

Background Information on ICCVAM and NICEATM

ICCVAM is an interagency committee composed of representatives from 15 Federal regulatory and research agencies that use or generate toxicological information. ICCVAM conducts technical evaluations of new, revised, and alternative methods with regulatory applicability and promotes the scientific validation and regulatory acceptance of toxicological test methods that more accurately assess the safety and hazards of chemicals and products and that refine, reduce, or replace animal use. The ICCVAM Authorization Act of 2000 (42 U.S.C. 285) established ICCVAM as a permanent interagency committee of the NIEHS under the NICEATM. NICEATM administers the ICCVAM and provides scientific and operational support for ICCVAM-related activities. NICEATM and ICCVAM work collaboratively to evaluate new and improved test methods applicable to the needs of Federal agencies. Additional information about ICCVAM and NICEATM can be found at the following Web site: *http://iccvam.niehs.nih.gov*.

Dated: October 5, 2006.

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