DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institute of Environmental Health Sciences (NIEHS); National Toxicology Program (NTP); Notice of Availability of the Report: ''Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Evaluation of In Vitro Test Methods for Detecting Potential Endocrine Disruptors: Estrogen Receptor and Androgen Receptor Binding and Transcriptional Activation Assays''

Summary

The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) announces the availability of the report entitled, ''ICCVAM Evaluation of In Vitro Test Methods for Detecting Potential Endocrine Disruptors: Estrogen Receptor and Androgen Receptor Binding and Transcriptional Activation Assays,'' NIH Publication 02–4503. The report contains ICCVAM's recommendations on minimum procedural standards and reference substances for standardization and validation of in vitro estrogen and androgen receptor binding and transcriptional activation assays.

Availability of Report

The report is available electronically (PDF format) on the NICEATM/ICCVAM web site at *http://iccvam.niehs.nih.gov.* A limited number of printed reports and CDs are available. To receive a printed report or CD, please send a request to Dr. William S. Stokes, Director, NICEATM, PO Box 12233, MD EC–17, Research Triangle Park, NC 27709, phone: 919–541–2384, fax: 919–541–0947, or email *niceatm@niehs.nih.gov.* Inquiries about the report or its availability should be sent to Dr. Stokes at the above address.

Background

In April 2000, the EPA asked the ICCVAM to evaluate the validation status of in vitro estrogen receptor (ER) and androgen receptor (AR) binding and transcriptional activation (TA) assays that were proposed as possible components of the EPA Endocrine Disruptor Screening Program (EDSP) Tier 1 screening battery. ICCVAM, which is charged by law (Pub. L. 106–545) to evaluate the scientific validity of new, revised, and alternative test methods proposed for specific regulatory uses, agreed to evaluate these test methods based on their potential interagency applicability and public health significance.

The NICEATM, which administers and provides scientific support for the ICCVAM, subsequently compiled available data and information on in vitro ER and AR binding and TA assays. Four draft Background Review Documents (BRDs) (available at *http://iccvam.niehs.nih.gov/methods/endocrine.htm*) were prepared according to published guidelines for submission of test methods to ICCVAM (ICCVAM 1999). This comprehensive review found that there are no adequately standardized and validated in vitro ER- or AR-based test methods. The NICEATM proposed minimum procedural standards that should be incorporated into standardized protocols for each of the four types of assays. In addition, NICEATM included within each BRD a list of proposed substances that should be used for the validation of in vitro ER and AR binding and TA assays.

In collaboration with the ICCVAM Endocrine Disruptor Working Group (EDWG), NICEATM organized an independent technical evaluation of the four types of in vitro endocrine disruptor test methods on May 20–21, 2002 in Research Triangle Park, NC [**Federal Register**. 66 FR 57: 16278–16279, March 23, 2001 and 67 **Federal Register** 66: 16415–16416, April 5, 2002). This meeting was open to the public with time set aside for public comment.

A 24-member scientific expert panel reviewed the information and recommendations provided in the four draft BRDs and developed its own conclusions and recommendations for each type of test method on the following:

- Specific test methods that should undergo further evaluation in validation studies and their relative priority for evaluation;
- The adequacy of the proposed minimum procedural standards;
- The adequacy of protocols for specific test methods recommended for validation; and
- The adequacy and appropriateness of substances proposed for validation studies.

The expert panel presented its evaluations, conclusions, and recommendations at the meeting. Following the meeting, the expert panel's written evaluations and consensus recommendations were consolidated into an independent report (*http://iccvam.niehs.nih.gov/methods/endocrine.htm*).

In October 2002 (67 FR 204: 64902–64903, October 22, 2002), the NICEATM made available for public comment the expert panels' final report. This report contains the expert panel's evaluations and consensus recommendations for the four types of assays and a revised list of proposed substances for validation of in vitro ER and AR binding and TA test methods. Following review of this report and the public comments, ICCVAM finalized its recommendations and developed recommended minimum procedural standards and the list of proposed substances that should be used to standardize and validate in vitro ER and AR binding and TA assays. The final expert panel report, public comments, and other relevant documents are appended to the ICCVAM report. The ICCVAM report, whose availability is announced in this notice (see above), will be forwarded to Federal agencies for their consideration and information.

The minimum procedural standards and the list of recommended substances for validation should facilitate standardization and validation of in vitro endocrine disruptor assays. Data from validation studies on test methods that incorporate the recommended minimum procedural standards will serve as the basis for developing minimum performance standards for acceptable in vitro ER-or AR-based test methods. The EDSP will use data generated from validated in vitro and in vivo Tier 1 screening test methods to reach weight-of-evidence decisions on whether to conduct large multi-generational in vivo studies. It is also anticipated that data obtained during the validation of the four different types of in vitro ER- and AR-based test methods will help characterize the extent to which individual or batteries of in vitro endocrine disruptor test methods might be used to prioritize chemicals for Tier 1 screening and Tier 2 testing. Finally, implementation of the recommendations in this report is expected to decrease and perhaps eventually eliminate the need to use male and female animals as a source of AR and ER, respectively, for in vitro screening assays.

Test method developers are encouraged to submit in vitro test methods for evaluation by ICCVAM that adhere to the minimum procedural standards outlined in this report and that have undergone validation using the recommended substances. Following adequate validation of in vitro endocrine disruptor test methods, ICCVAM and NICEATM will coordinate their scientific peer review. Formal ICCVAM test recommendations will then be forwarded to Federal agencies as required by the ICCVAM Authorization Act of 2000 (Pub. L. 106–545).

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