
DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Toxicology Program (NTP); NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Evaluation of In Vitro Estrogen Receptor Transcriptional Activation and In Vitro Cell Proliferation Assays for Endocrine Disruptor Chemical Screening: Request for Nominations for an Independent Expert Peer Review Panel and Submission of Relevant In Vitro and In Vivo Data

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

ACTION: Request nominations for an independent expert panel and submission of relevant data.

SUMMARY: NICEATM, in collaboration with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), is planning to convene an independent scientific peer review panel (hereafter, Panel) to assess the validation status of an *in vitro* stably-transfected estrogen

receptor (ER) transcriptional activation (TA) Assay (LUMI-CELL® ER assay) and an *in vitro* cell proliferation assay (CertiChem MCF-7 Cell Proliferation assay) for their usefulness and limitations in determining whether and to what extent chemicals can interact with estrogen receptors *in vitro*.

Validated assays that can detect the interaction of chemicals with specific hormone receptors including the ER are included in the U.S. Environmental Protection Agency (EPA) Endocrine Disruptor Screening Program (EDSP) (<http://www.epa.gov/endo/pubs/assayvalidation/status.htm>). The two assays that will undergo peer review are currently undergoing validation studies to determine their usefulness and limitations for the EDSP. Any other existing data from these two assays are requested to ensure that all available relevant data are considered by the Panel. Data from other existing *in vitro* and *in vivo* assays for the 78 reference substances used for the validation studies (available at http://iccvam.niehs.nih.gov/docs/endo_docs/EDAddendFinal.pdf) are requested for use in characterizing the expected *in vitro* and *in vivo* activity of these 78 reference substances. At this time NICEATM requests:

- Nominations of expert scientists for consideration as potential Panel members.

- Submission of existing data from the LUMI-CELL® ER and the CertiChem MCF-7 Cell Proliferation assays.

- Submission of data from *in vivo* or other *in vitro* assessments for the 78 reference substances recommended by ICCVAM for the validation of *in vitro* ER and AR binding and TA test methods (available at http://iccvam.niehs.nih.gov/docs/endo_docs/EDAddendFinal.pdf).

DATES: Submit nominations and data by January 11, 2010. Data submitted after this date will be considered in the evaluation, where feasible.

ADDRESSES: Submit nominations and data electronically by e-mail to niceatm@niehs.nih.gov, or via the NICEATM-ICCVAM Web site at http://iccvam.niehs.nih.gov/contact/FR_pubcomment.htm. Nominations and data may also be sent by mail or fax to 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, (e-mail). Courier address: NIEHS, NICEATM, 530 Davis Drive, Room 2034, Morrisville, NC 27560.

FOR FURTHER INFORMATION CONTACT: Dr. William S. Stokes, (telephone) 919-541-2384, (fax) 919-541-0947 and (e-mail) niceatm@niehs.nih.gov.

SUPPLEMENTARY INFORMATION:

Background

In April 2000, the EPA requested that ICCVAM evaluate the validation status of *in vitro* ER and AR binding and TA assays for potential use in the proposed EPA EDSP. ICCVAM and NICEATM compiled available relevant data for 137 existing assays and compiled data were submitted to an independent expert panel for review. This panel concluded that there were no adequately validated *in vitro* ER- or AR-based test methods (the panel's report is available on the NICEATM-ICCVAM Web site at http://iccvam.niehs.nih.gov/methods/endocrine/end_EPrpt.htm). Based on these conclusions and recommendations, along with comments from the public, ICCVAM recommended minimum procedural standards and a list of 78 reference substances that should be used to standardize and validate *in vitro* ER and AR binding and TA test method protocols. These recommendations were made publicly available in the report: *ICCVAM Evaluation of the In Vitro Methods for Detecting Potential Endocrine Disruptors: Estrogen Receptor and Androgen Receptor Binding and Transcriptional Activation Assays* (available at: http://iccvam.niehs.nih.gov/methods/endocrine/end_TMER.htm). The list of 78 reference substances was subsequently modified because of cost and availability considerations and published in a separate Addendum (available at: http://iccvam.niehs.nih.gov/docs/endo_docs/EDAddendFinal.pdf).

Two *in vitro* assays to detect ER agonists and antagonists were subsequently nominated to ICCVAM for validation studies in response to an ICCVAM request (69 FR 21564): The LUMI-CELL® ER assay developed by Xenobiotic Detection Systems, Inc. (XDS) and the CertiChem MCF-7 Cell Proliferation assay developed by CertiChem, Inc. (CertiChem). Based on preliminary results provided for these test methods and comments from the public and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM; 69 FR 21564 and 71 FR 60748, respectively), ICCVAM and its Endocrine Disruptor Working Group recommended a high priority for validation studies for the LUMI-CELL® ER and CertiChem MCF-7 Cell Proliferation assays.

An international interlaboratory validation study of the LUMI-CELL® ER assay is currently nearing completion. The study includes three laboratories sponsored by NICEATM, the European Centre for the Validation of Alternative Methods, and the Japanese Center for the Validation of Alternative Methods. An intralaboratory validation study of the MCF-7 Cell Proliferation assay has been completed by CertiChem in conjunction with NICEATM, and an interlaboratory study is planned.

NICEATM will prepare draft background review documents (BRDs) following completion of the validation studies that will provide comprehensive summaries of available data, analyses of test method accuracy and reliability, and related information characterizing the current validation status of each of the assays. The draft BRDs will form the basis for draft ICCVAM test method recommendations on usefulness and limitations, standardized test method protocols, future studies, and performance standards that will subsequently be provided to the Panel and made available to the public. The Panel will meet in public session to review the validation status of the LUMI-CELL® ER, MCF-7 Cell Proliferation assays, and any of the other assays for which there are adequate data available. The Panel will comment on the extent to which the BRD supports draft ICCVAM test method recommendations. The Panel may also consider the results for other assays with incomplete validation databases to determine their current validation status and to identify data gaps that need to be addressed in order to further characterize their usefulness and limitations for the EDSP. Meeting information, including dates, locations, and public availability of the BRDs will be announced in future **Federal Register** notices and will also be posted on the ICCVAM/NICEATM Web site (http://iccvam.niehs.nih.gov/methods/endocrine/end_eval.htm).

Request for Nominations of Scientific Experts

NICEATM requests nominations of scientists with relevant knowledge and experience to serve on the Panel. Areas of relevant expertise include, but are not limited to, biostatistics, cellular biology, endocrinology, molecular genetics, regulatory toxicology, reproductive toxicology, and test method validation. Each nomination should include the nominee's name, affiliation, contact information (*i.e.*, mailing address, email address, telephone, and fax numbers), *curriculum vitae*, and a brief summary

of relevant experience and qualifications.

Request for Data

NICEATM invites the submission of relevant *in vitro* and *in vivo* data and information for reference substances on the list of 78 substances recommended by ICCVAM for standardizing and validating *in vitro* ER and AR binding and TA test methods (available at http://iccvam.niehs.nih.gov/docs/endo_docs/EDAddendFinal.pdf) or other substances for which data exists from the two *in vitro* test methods described in this notice. Relevant *in vivo* data may include, but are not limited to: Multi-generational reproductive and developmental toxicity studies, uterotrophic bioassays, and short term assays assessing changes in phenotypic parameters such as anogenital distance, time of vaginal opening, nipple retention, and preputial separation delays in males.

Although data can be accepted at any time, data received by January 11, 2010 will ensure consideration during the ICCVAM evaluation process. Relevant data received after this date will be considered during the ICCVAM evaluation process where feasible. All information submitted in response to this notice will be made publicly available and may be incorporated into future NICEATM and ICCVAM reports and publications as appropriate.

When submitting data, please reference this **Federal Register** notice and provide appropriate contact information (name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization, as applicable).

NICEATM prefers that data be submitted as copies of pages from study notebooks and/or study reports, if available. Laboratory data and analyses available in electronic format may also be submitted. Each submission for a substance should preferably include the following information, as appropriate:

- Common and trade name
- Chemical Abstracts Service Registry Number (CASRN)
- Commercial source
- *In vivo* or *in vitro* test protocol used
- Individual animal or *in vitro* responses at each observation time (*i.e.*, laboratory data)
 - The extent to which the data were collected in accordance with national/international Good Laboratory Practice guidelines
 - Date and testing organization
 - Physical and chemical properties (*e.g.*, molecular weight, pH, water solubility, *etc.*)

Background Information on ICCVAM, NICEATM, and SACATM

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, and replace animal use. The ICCVAM Authorization Act of 2000 (42 U.S.C. 2851-3, available at http://iccvam.niehs.nih.gov/docs/about_docs/PL106545.pdf) 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. 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 is available on the NICEATM-ICCVAM Web site: <http://iccvam.niehs.nih.gov>.

SACATM was established January 9, 2002 and is composed of scientists from the public and private sectors (67 FR 11358). SACATM provides advice to the Director of the NIEHS, ICCVAM, and NICEATM regarding the statutorily mandated duties of ICCVAM and activities of NICEATM. Additional information about SACATM, including the charter, roster, and records of past meetings, can be found at <http://ntp.niehs.nih.gov/go/167>.

Dated: November 16, 2009.

John R. Bucher,

Associate Director, National Toxicology Program.

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