DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH), National Toxicology Program (NTP); Request for Data and Nominations of Expert Scientists for an Independent Peer Review Evaluation of In Vitro Estrogen and Androgen Receptor Binding and Transcriptional Activation Assays for Endocrine Disruptor Screening

SUMMARY: The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) in collaboration with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) is planning an independent Peer Review Panel (hereafter, Panel) evaluation of the validation status of in vitro estrogen receptor (ER) and androgen receptor (AR) binding and transcriptional activation assays. Conclusions and recommendations from the Panel will be considered by federal agencies in selecting and establishing minimum performance criteria for in vitro test methods used to screen chemicals for potential endocrine disrupting effects, including the U.S. Environmental Protection Agency's (EPA) Endocrine Disruptor Screening Program. At this time, NICEATM requests study results and data evaluating the performance and reliability of ER and AR binding and transcriptional activation assays, and other relevant information from the scientific community that should be considered by the Panel. NICEATM also requests nominations of expert scientists for consideration as potential Panel members.

BACKGROUND INFORMATION: In response to public concern that pesticides may interfere with endocrine processes in humans and wildlife, Congress directed EPA, through the 1996 Food Quality Protection Act (FQPA) (Pub. L. 104–170) to develop a screening program for evaluating the potential of pesticides and other chemicals to induce hormone-related health effects. Language in the1996 amendments to the Safe Drinking Water Act (Pub. L. 104–182) added that EPA would use this screening program to evaluate substances found in drinking water sources for endocrine effects if there is widespread human exposure to such substances. Consequently, in 1998, EPA proposed an Endocrine Disruptor Screening Program (EDSP) (**Federal Register**, Vol. 63, No. 248, pp. 71541–71568, December 28, 1998, available at *http://www.epa.gov/fedrgstr/EPA–TOX/1998/December/Day-28/t34298.htm*).

The conceptual framework of the EDSP (*http://www.epa.gov/scipoly/oscpendo/index.htm*) consists of a Tier 1 Screening battery of tests that is designed to identify substances capable of interacting with the endocrine system, and a Tier 2 Testing level that is designed to confirm Tier 1 results and characterize the nature of the endocrine disrupting effects of the substances identified with Tier 1 Screening. Under the mandates of the FQPA, EPA is requiring that each screen and test method proposed for use in the program undergo standardization and scientific validation consistent with the principles of ICCVAM, as described in NIH Publication 97–3981, Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM Report), available at *http://iccvam.niehs.nih.gov/validate.pdf* and the Organization for Economic Co-operation and Development (OECD) (Final Report of the OECD Workshop on Harmonization of Validation and Acceptance Criteria for Alternative Toxicological Test Methods: OECD, 1996, available at *http://www.oecd.org//ehs/test/08e69840.pdf*).

EPA nominated the ER and AR binding assays and ER and AR transcriptional activation assays for review using the ICCVAM evaluation process, and agreed to sponsor the necessary background review document preparation and peer review. ICCVAM subsequently recommended that these methods should undergo independent scientific peer review based on their potential interagency applicability and public health significance. NICEATM, in collaboration with ICCVAM, is therefore convening an independent panel of scientists to assess the validation status of these four different types of in vitro assays. These assays are relevant for screening purposes in the EDSP because they may identify substances that alter natural endocrine processes in the body by binding with estrogen and/or androgen receptors, resulting in either activation or

inhibition of gene activation. As part of the evaluation, EPA requested the development and review of proposed minimum performance criteria that future methods of these types should achieve, in light of the performance of existing methods.

For both the receptor binding and transcriptional activation assays, the Panel will evaluate the extent to which the validation and acceptance criteria outlined in the ICCVAM Report have been addressed. The Panel will be asked to provide conclusions and recommendations regarding the usefulness and limitations of various ER and AR binding and/or transcriptional activation assays, and the adequacy of proposed technically feasible minimum performance criteria that these types of assays should achieve. Finally, the Panel will address whether and what additional test method development and validation efforts might further enhance and/or characterize the usefulness of specific in vitro ER and AR binding and/or transcriptional activation assays.

NICEATM is preparing background review documents on ER and AR binding and transcriptional activation testing methods that will contain comprehensive summaries of available data and related information characterizing the current validation status of these assays. The Panel will evaluate the background review documents, which will also be made available to the public.

The Peer Review Panel meeting is anticipated to take place in early 2002. Meeting information, including date and location, and public availability of the background review documents will be announced in a future **Federal Register** notice that will also be posted on the ICCVAM/NICEATM website (*http://iccvam.niehs.nih.gov*).

Request for Nominations of Experts to Serve on the Panel

NICEATM invites nominations of scientists with relevant knowledge and experience who might be considered for the independent Peer Review Panel. Areas of expertise that may be relevant include, but are not limited to, endocrinology, reproductive toxicology, cellular biology, molecular genetics and biostatistics. Each nomination should include the person's name, affiliation, contact information (i.e., mailing address, telephone and fax numbers, and e-mail address), and a brief summary of relevant experience and qualifications. Nominations should be sent to NICEATM by mail, fax or e-mail within 60 days of the publication date of this notice. Correspondence should be directed to Dr. William S. Stokes, Director, NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, NIEHS, 79 T.W. Alexander Drive, MD EC–17, P.O. Box 12233, Research Triangle Park, NC 27709; telephone: 919–541–7997; fax: 919–541–0947; e-mail: iccvam@niehs.nih.gov.

Request for Data

NICEATM welcomes data from completed studies using or evaluating ER and AR binding and/or transcriptional activation assays, and information about ongoing or planned studies using these methods. Information should address applicable aspects of the validation and regulatory acceptance criteria provided in the ICCVAM Report. Where possible, data and information should adhere to the guidance provided in NIH Publication 99–4496, Evaluation of the Validation Status of Toxicological Methods: General Guidelines for Submissions to ICCVAM (*http://iccvam.niehs.nih.gov/subguide.htm*). Both documents are available by request from NICEATM at the address provided above. Information and data should be submitted within 60 days of the publication date of this notice to ensure adequate consideration during preparation of the background review documents for the Panel. Correspondence should be sent by mail, fax or e-mail to Dr. William S. Stokes (contact information is provided in the previous section of this notice).

Background Information on ICCVAM and NICEATM

ICCVAM was established in 1997 to coordinate cross-agency issues relating to the validation, acceptance, and national/international harmonization of toxicological testing methods. Composed of representatives from fifteen Federal regulatory and research agencies that use or generate toxicological information, ICCVAM promotes the scientific validation and regulatory acceptance of toxicological test methods that enhance agencies' ability to make decisions on health risks, while refining, reducing, and replacing animal use wherever possible. ICCVAM was authorized as a permanent Federal committee on December 19, 2000 through passage of the ICCVAM Authorization Act of 2000 (Pub. L. 106–545, available at *http://iccvam.niehs.nih.gov/PL106545.htm*). NICEATM provides operational and scientific support for ICCVAM and ICCVAM-related activities. NICEATM and ICCVAM work collaboratively to develop, validate, and achieve regulatory acceptance of new and improved test methods applicable to the needs of Federal agencies.

Additional information about ICCVAM and NICEATM can be found at the following website: *http://iccvam.niehs.nih.gov*.

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