DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Toxicology Program (NTP), NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Notice of Availability of a Revised List of Recommended Reference Substances for Validation of In Vitro Estrogen and Androgen Receptor Binding and Transcriptional Activation Assays: Request for Comments and Submission of In Vivo and In Vitro Data

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

ACTION: Request for Comments and Submission of Data.

SUMMARY: The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) announces the availability of an addendum to the report entitled, ''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'' [NIH Publication 03–4503]. The addendum describes the rationale for proposed revisions to the original list of recommended reference substances for validation of *in vitro* estrogen receptor (ER) and androgen receptor (AR) binding and transcriptional activation (TA) assays. The original list was made publicly available in June 2003 (**Federal Register**, Vol. 68, No. 106, pp. 33171–33172, June 3, 2003). NICEATM requests public comments on the substances proposed as substitutes for six of the 78 substances in the original list. Data are also requested from *in vitro* and *in vivo* studies evaluating the estrogenic and androgenic activity of the 78 substances in the revised list of reference substances.

DATES: Comments and data submissions should be received by May 1, 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 April 2000, the Environmental Protection Agency (EPA) asked ICCVAM to evaluate the validation status of *in vitro* ER and AR binding and TA assays that were proposed as possible components of the EPA Endocrine Disruptor Screening Program Tier 1 screening battery. ICCVAM agreed to evaluate these test methods based on their potential interagency applicability and public health significance. NICEATM, which administers and provides scientific support for ICCVAM, subsequently compiled available data and information on in vitro ER and AR binding and TA assays in four draft Background Review Documents (BRDs) (available at *http://iccvam.niehs.nih.gov/methods/endocrine.htm*).

In collaboration with the ICCVAM Endocrine Disruptor Working Group, NICEATM organized an independent scientific evaluation of the validation status of the four types of in vitro endocrine disruptor screening test

methods on May 20–21, 2002, in Research Triangle Park, NC (**Federal Register**, Vol. 66, No. 57, pp. 16278–16279, March 23, 2001 and **Federal Register**, Vol. 66, No. 67, pp. 16415–16416, April 5, 2002) (available at *http://iccvam.niehs.nih.gov/methods/endocrine.htm*).

The final BRDs and the ICCVAM Test Method Evaluation Report, which includes the expert panel report, public comments, and other relevant documents, were published in May 2003 and announced in a **Federal Register** notice (Vol. 68, No. 106, pp. 33171–33172, June 3, 2003) (available at *http://iccvam.niehs.nih.gov/methods/endocrine.htm*).

NICEATM recently reviewed the commercial availability and cost for the 78 substances recommended by ICCVAM for use in *in vitro* ER and AR binding and TA validation studies. A minimum of 44 substances are recommended for AR binding and TA assays, while a minimum of 53 substances are recommended for ER binding and TA assays. This review indicated that three substances [anastrazole, CGS 18320B, fadrozole] are not commercially available, one substance has restricted commercial availability [ICI 182,780] and six others [actinomycin D, hydroxyflutamide, 4-hydroxytamoxifen, methyltrienolone, 12-O-tetradecanoylphorbol-13-acetate, zearalenone] have costs that are considered excessive. ICCVAM proposes replacing the four substances that are not commercially available or have restricted availability with ones having similar ER and AR activity profiles [4-hydroxyandrostenedione, chrysin, dicofol, raloxifene HCl]. Suitable replacements (19-nortestosterone and resveratrol) were identified for metyltrienolone and zearalenone, respectively, for two of the expensive substances. NICEATM would also prefer to replace four of the highly priced substances [actinomycin D, hydroxyflutamide, 4-hydroxytamoxifen, 12-O-tetradecanoy.lphorbol-13-acetate], but has been unable to identify suitable replacements because of their unique activity profiles and/or chemical/physical properties. The revised list of 78 substances and a discussion about the proposed revisions are included and discussed in the ''Addendum to the ICCVAM Evaluation of In Vitro Test Methods for Detecting Potential Endocrine Disruptors: Estrogen Receptor and Androgen Receptor Binding and Transcriptional Activation Assays,'' (available at *http://iccvam.niehs.nih.gov* see ''Test Method Evaluations'') or by contacting NICEATM (see **ADDRESSES** above.) ICCVAM will finalize this list after considering any public comments received and forward it to U.S. Federal agencies for their information and consideration.

Request for Comments and Request for Data

NICEATM requests public comments on the four substances (listed above) proposed as replacements for substances on the list that are not readily commercially available. NICEATM also requests public comments on the proposed replacements for the two expensive substances for which replacements have been identified, and suggestions for replacements for the four expensive substances that remain on the recommended list.

In order to update the reference substance database, NICEATM request data from completed *in vitro* studies using or evaluating ER and AR binding and/or TA assays, and information about ongoing or planned studies using or evaluating these test methods. NICEATM also requests the submission of data from animal studies that have evaluated the endocrine activity of chemicals using, for example, the uterotropic, Hershberger, intact male, or male/female pubertal assays. NICEATM is especially interested in receiving additional data or information on any of the 78 substances included in the reference list. NICEATM previously requested data from completed studies using or evaluating ER and AR binding and/or TA assays, and information about ongoing or planned *in vitro* or *in vivo* studies using or evaluating these test methods (**Federal Register**, Vol. 66, No. 57, pp. 16278–16279, March 23, 2001). Submitted data will be used to update and supplement the existing NICEATM database; the current database can be accessed in the ICCVAM Test Method Evaluation Report [NIH Publication No. 03–4503] and the four final BRDs on ER and AR binding and TA assays [NIH Publication No. 03–4504, 03–4505, 03–4506, and 03–4507] (available at *http://iccvam.niehs.nih.gov/methods/endocrine.htm*).

When submitting chemical and protocol information/test 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 data to be submitted as copies of pages from study notebooks and/or study reports, if available. Raw data and analyses available in electronic format may also be submitted. If data are published in the peer-reviewed literature, citations should be provided. Each submission for a chemical should preferably include the following information, as appropriate:

- Common and trade name
- Chemical Abstracts Service Registry Number (CASRN)
- Chemical class
- Product class
- Commercial source
- *In vitro* test protocol used
- *In vitro* test results
- *In vivo* test protocol used
- *In vivo* test results
- The extent to which the study complied with national or international Good Laboratory Practice (GLP) guidelines
- Date and testing organization

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 (Pub. L. 106–545) establishes 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://www.iccvam.niehs.nih.gov.*

Dated: March 7, 2006.

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