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 a Revised List of Recommended Reference Substances for Validation of In Vitro Estrogen and Androgen Receptor Binding and Transcriptional Activation Assays

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

ACTION: Notice of the availability of a revised list of recommended reference substances.

SUMMARY: NICEATM announces the availability of an addendum to 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'' [NIH Publication 03–4503]. The addendum describes the rationale for 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.

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 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 the **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, and 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 has replaced the four substances, which are not commercially available or have restricted availability, with ones having similar ER and AR activity profiles (4-hydroxyandrostenedione, chrysin, dicofol, raloxifene HCl). 19-nortestosterone and resveratrol were identified as replacements for two of the expensive substances, metyltrienolone and zearalenone respectively. NICEATM sought to replace four of the highly priced substances (actinomycin D, hydroxyflutamide, 4-hydroxytamoxifen, 12-O-tetradecanoylphorbol-13-acetate), but was unable to identify suitable replacements because of their unique activity profiles and/or chemical/physical properties. The proposed revisions were made available for public comment in March 2006 (**Federal Register,** Vol. 71, No. 51, pp. 13597–13598, March 16, 2006) and no comments were received. The final revised list of 78 reference substances recommended for validation of *in vitro* ER and AR binding and TA validation studies and a discussion about the revisions are now available in the document, ''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.'' The addendum is available on the ICCVAM/NICEATM Web site at *http://iccvam.niehs.nih.gov* see ''Test Method Evaluations'' or by contacting NICEATM (requests 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*.).

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) 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: September 18, 2006.

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[FR Doc. E6–15972 Filed 9–27–06; 8:45 am]

BILLING CODE 4140–01–P