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); Nomination To Hold a Workshop on Alternative Methods To Replace the Mouse LD_{50} Assay for Botulinum Toxin Potency Testing: Request for Comments, Nominations of Experts, 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, nominations of scientific experts, and submission of data.

SUMMARY: In October 2005, the Humane Society of the United States (HSUS) submitted a nomination to NICEATM requesting that alternative test methods to the mouse LD_{50} assay for botulinum toxin potency testing be assessed and prioritized for prevalidation and validation efforts. The nomination proposed that an initial key step in this process would be for the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) to organize a workshop on this topic. ICCVAM considered the nomination and supports with a high priority the concept of a workshop to discuss alternative methods and approaches that might reduce, refine, or replace the use of animals for botulinum potency testing. The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) considered the nomination and the ICCVAM proposal at its meeting on December 12, 2005, and agreed that the proposed activity should have a high priority. At this time, NICEATM requests (1) information on development and/or validation activities relevant to reduction, refinement (less pain and distress), and/or replacement alternatives for botulinum toxin potency testing, (2) public comments on the appropriateness and relative priority of proceeding with a workshop on this topic, (3) the nomination of scientific experts who might participate if a workshop occurs, and (4) the submission of data from mouse LD_{50} botulinum potency testing and *ex vivo* and *in vitro* test methods used for botulinum toxin potency testing. The HSUS nomination is available at *http://iccvam.niehs.nih.gov/* see ''Nominations and Submissions.''

DATES: Comments, nominations of expert scientists, and data submissions should be received by March 13, 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 October 2005, the HSUS submitted a nomination to NICEATM to organize a workshop to evaluate the state-of-the-science for potential alternatives to the mouse LD_{50} assay for botulinum toxin potency testing. The HSUS nomination is available at *http://iccvam.niehs.nih.gov/* see ''Nominations and Submissions.'' ICCVAM considered the nomination and supports the concept of a workshop to discuss alternative methods and approaches that might reduce, refine, or replace the use of animals for botulinum potency testing with a high priority. The SACATM discussed this nomination at its meeting on December 12, 2005, and advised NICEATM and ICCVAM that they consider the development and validation of alternatives to the mouse LD_{50} assay for botulinum toxin potency testing a high priority. SACATM also suggested that prior to convening a workshop that ICCVAM and NICEATM find out what efforts toward developing or validating alternatives might already be underway by companies that conduct botulinum potency testing. NICEATM now seeks (1) information on any activities directed at the development and/or validation of alternatives to the mouse LD_{50} assay for botulinum toxin potency testing, (2) input from the public on this nomination for a workshop, (3) the nomination of scientific experts who might participate in any future workshop on this topic should it occur, as well as (4) data from mouse LD_{50} botulinum potency testing and *ex vivo* and *in vitro* test methods used for botulinum toxin potency testing. NICEATM and ICCVAM will consider this information and determine how to best move forward with this nomination.

Request for Comments, Nominations of Scientific Experts and Request for Data

NICEATM requests information on the status of any efforts to develop alternatives to the mouse LD_{50} assay for botulinum toxin potency testing, as well as public comments on the appropriateness and relative priority of the proposed workshop activity. In addition, NICEATM requests the nomination of scientists with relevant knowledge and experience to potentially participate in the workshop should it be held. Areas of relevant expertise include, but are not limited to: neurophysiology, neuropharmacology, neurotoxicity, immunology, potency testing of toxins and other biologicals in animals and *in vitro* systems, development and use of *in vitro* methodologies, and biostatistical data analysis. Each nomination should include the person's name, affiliation, contact information (*i.e.*, mailing address, e-mail address, telephone and fax numbers), and a brief summary of relevant experience and qualifications.

NICEATM invites the submission of data from *in vivo* botulinum toxin potency testing, including clinical observations and corresponding time-course information, and information and data from *ex vivo* and *in vitro* test methods being used as potential alternatives to the mouse assay for botulinum toxin potency testing. Submitted data will be used to further evaluate the usefulness and limitations of *in vitro* potency test methods and may be included in future NICEATM and ICCVAM reports and publications as appropriate. The data will also be included in a NICEATM database to support the investigation of alternative test methods for assessing potency of botulinum toxin.

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. Each submission should preferably include the following information, as appropriate:

- Specific type of botulinum neurotoxin tested (*e.g., Clostridium botulinum* neurotoxin type A)
- *In vivo* potency test protocol used.
- *In vivo* potency test results.
- Individual animal responses, including time of onset of specific clinical signs and death.
- Alternative *ex vivo* or *in vitro* test protocol used.
- Alternative *ex vivo* or *in vitro* test results.
- The extent to which the study complied with national or international Good Laboratory Practice (GLP) guidelines.
- Date of the study.
- The organization that conducted the study.

Although public comments and data can be accepted at any time, information submitted by the deadline listed in this notice would be most useful for determining whether a workshop is the appropriate next step in pursuing an alternative to the mouse LD_{50} assay for botulinum toxin potency testing. In addition, submitting information by this date ensures its availability to workshop participants if a workshop is held.

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, 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*.

The SACATM, established January 9, 2002, is a federally chartered advisory committee composed of scientists from the public and private sectors (**Federal Register**: March 13, 2002: Vol. 67, No. 49, page 11358). The SACATM provides advice to the Director of the NIEHS, ICCVAM, and NICEATM regarding 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/*, see ''Advisory Board & Committees.''

Dated: January 17, 2006.

Samuel H. Wilson,

Deputy Director, National Institute of Environmental Health Sciences.

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