DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Toxicology Program (NTP), NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Announcement of an Independent Scientific Peer Review Meeting on the Use of In Vitro Testing Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Tests and Request for Comments

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

ACTION: Meeting Announcement and Request for Comment.

SUMMARY: NICEATM in collaboration with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) announces a public, independent, scientific peer review meeting to evaluate the validation status of the *in vitro* 3T3 and normal human keratinocyte (NHK) neutral red uptake (NRU) basal cytotoxicity test methods for estimating starting doses for *in vivo* acute oral toxicity tests. These two *in vitro* cytotoxicity test methods are proposed as adjuncts to the *in vivo* acute oral toxicity tests to refine (i.e., to lessen or avoid pain and distress) and/or reduce animal use. At this meeting, a scientific peer review panel (''Panel'') will peer review the background review document (BRD) on the 3T3 and NHK cytotoxicity test methods, evaluate the extent that the BRD addresses established validation and acceptance criteria, and provide comment on the draft ICCVAM recommendations on the proposed use of these test methods, draft test method protocols, and draft performance standards. NICEATM requests public comments on the BRD, draft ICCVAM test method recommendations, draft test method protocols, and draft performance standards.

DATES: The meeting will be held on May 23, 2006, from 8:30 a.m. to 5 p.m. The meeting is open to the public with attendance limited only by the space available. In order to facilitate planning for this meeting, persons wishing to attend the meeting are asked to register via the ICCVAM/NICEATM Web site (*http://iccvam.niehs.nih.gov*) by May 12, 2006.

ADDRESSES: The meeting will be held at the National Institutes of Health (NIH), Natcher Conference Center, 45 Center Drive, Bethesda, MD 20892.

FOR FURTHER INFORMATION CONTACT: Correspondence should be sent by mail, fax, or email 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*, Courier address: NICEATM, 79 T.W. Alexander Drive, Building 4401, Room 3128, Research Triangle Park, NC 27709.

SUPPLEMENTARY INFORMATION:

Background

In September 2001, ICCVAM recommended that *in vitro* basal cytotoxicity test methods be considered as tools for estimating starting doses for *in vivo* acute systemic toxicity studies (**Federal Register** Vol. 66, No. 189, pp. 49686–7, September 28, 2001). The recommendations were based on the *Report of the International Workshop on In Vitro Methods for Assessing Acute Systemic Toxicity* (ICCVAM, 2001a). The *Guidance Document on Using In Vitro Data to Estimate In Vivo Starting Doses for Acute Toxicity* (ICCVAM, 2001b) was also made available at that time. The guidance document provided standard procedures for two *in vitro* basal cytotoxicity test methods and instructions for using these test methods to estimate starting doses for *in vivo* testing.

U.S. Federal agencies' responses to the ICCVAM recommendations from the International Workshop were announced in 2004 (**Federal Register** Vol. 69, No. 47, pp. 11448–9, March 10, 2004). The U.S. Federal agencies agreed to encourage, to the extent applicable, the use of *in vitro* tests for determining starting doses for acute oral systemic toxicity testing. Furthermore, the U.S. Environmental Protection Agency (EPA) specifically encouraged those participating in the High Production Volume Challenge Program to consider using the recommended *in vitro* test methods as a supplemental component when conducting any new *in vivo* acute oral toxicity studies for the program (*http://www.epa.gov/chemrtk/toxprtow.htm*).

In 2002, NICEATM and the European Committee on the Validation of Alternative Methods began a collaborative validation study to independently evaluate the usefulness of two *in vitro* basal cytotoxicity test methods proposed for estimating starting doses for *in vivo* rodent acute oral toxicity tests. *In vitro* NRU cytotoxicity test methods using either BALB/c 3T3 fibroblasts, a mouse cell line, or NHK cells, primary human epidermal cells, were evaluated in a multi-laboratory international validation study. During the pre-validation phases of the study, the test method protocols were standardized further and revised to improve their intra- and inter-laboratory reproducibilities. NICEATM recommended using the revised test method protocols (**Federal Register**, Vol. 69, No. 201, pp. 61504–5, October 19, 2004) rather than the standard procedures outlined in the guidance document (ICCVAM, 2001b). During the validation study, 72 reference chemicals were tested using the 3T3 and NHK NRU test methods. The *in vitro* NRU cytotoxicity test results were used to estimate acute oral LD_{50} values, which in turn were used to identify the starting doses for simulated acute oral toxicity testing using the Up-and-Down Procedure (UDP; EPA 2002; OECD 2001a) and the Acute Toxic Class method (ATC; OECD 2001b). The *in vivo* test simulations were used to compare the number of animals used and the number of deaths expected to occur when starting with the default starting doses versus using a starting dose based on *in vitro* cytotoxicity data.

To assist in an evaluation of the usefulness of these two *in vitro* NRU basal cytotoxicity test methods for estimating starting doses for *in vivo*. acute oral toxicity tests, NICEATM requested the submission of existing *in vivo* and *in vitro* acute toxicity data (**Federal Register,** Vol. 69, No. 201, pp. 61504–5, October 19, 2004 and Vol. 65, No. 115, pp. 37400–3, June 14, 2000). In 2005, NICEATM announced a request for nominations of scientists to serve on the Panel and again requested existing *in vivo* and *in vitro* data (**Federal Register** Vol. 70, No. 54, pp. 14473–4, March 22, 2005).

Expert Panel Meeting

The purpose of this meeting is the scientific peer review evaluation of the validation status of the 3T3 and NHK NRU basal cytotoxicity test methods to determine starting doses for the UDP and ATC acute oral toxicity test methods in order to refine and reduce the use of animals. The Panel will first peer review the BRD on the 3T3 and NHK cytotoxicity test methods and then evaluate the extent that the BRDs address established validation and acceptance criteria (*Validation and Regulatory Acceptance of Toxicological Test Methods: A Report of the ad hoc Interagency Coordinating Committee on the Validation of Alternative Methods,* NIH Publication No. 97–3981, *http://iccvam.niehs.nih.gov*). The Panel will also be asked to provide comment on the draft ICCVAM test method recommendations, draft standardized test method protocols, and draft performance standards. Information about the Panel meeting, including a roster of the members of the Panel and the agenda, will be made available two weeks prior to the meeting on the ICCVAM/NICETATM Web site (*http://iccvam.niehs.nih.gov*) or can be obtained after that date by contacting NICEATM (see **FOR FURTHER INFORMATION CONTACT** above).

Attendance and Registration

The public Panel meeting will take place May 23, 2006, at the NIH Campus, Natcher Conference Center, Bethesda, MD (a map of the NIH Campus and other visitor information are available at *http://www.nih.gov/about/visitor/index.htm*). The meeting will begin at 8:30 a.m. and conclude at approximately 5 p.m. Persons needing special assistance, such as sign language interpretation or other reasonable accommodation in order to attend, should contact 919–541–2475 voice, 919–541–4644 TTY (text telephone), through the Federal TTY Relay System at 800–877–8339, or by e-mail to *niehsoeeo@niehs.nih.gov*. Requests should be made at least seven business days in advance of the event.

Availability of the BRD and Draft ICCVAM Recommendations

NICEATM prepared a BRD on the 3T3 and NHK NRU basal cytotoxicity test methods that contains comprehensive summaries of the data generated in the validation study, an analysis of the accuracy and reliability of the two test methods, a simulation analysis of the refinement and reduction in animal use that would occur if these tests were used as adjuncts to the UDP and ATC acute oral systemic toxicity test methods, and related information characterizing the validation status of these assays. The BRD, draft ICCVAM test method recommendations, draft test method protocols, and draft test method performance standards will be provided to the Panel and made available to the public. Copies of these materials can be obtained from the ICCVAM/NICEATM Web site (*http://iccvam.niehs.nih.gov*) or by contacting NICEATM (see **FOR FURTHER INFORMATION CONTACT** above).

Request for Comments

NICEATM invites the submission of written comments on the BRD, draft ICCVAM test method recommendations, draft test method protocols, and draft test method performance standards. When submitting written comments, it is important to refer to this **Federal Register** notice and include appropriate contact information (name, affiliation, mailing address, phone, fax, email and sponsoring organization, if applicable). Written comments should be sent by mail, fax, or email to Dr. William Stokes, Director of NICEATM, at the address listed above not later than May 5, 2006. All comments received will be placed on the ICCVAM/NICEATM website and made available to the Panel, ICCVAM agency representatives, and attendees at the meeting.

This meeting is open to the public and time will be provided for the presentation of public oral comments at designated times during the peer review. Members of the public who wish to present oral statements at the meeting (one speaker per organization) should contact NICEATM (see **FOR FURTHER INFORMATION CONTACT** above) no later than May 12, 2006. Speakers will be assigned on a consecutive basis and up to seven minutes will be allotted per speaker. Persons registering to make comments are asked to provide a written copy of their statement by May 12, 2006, so that copies can be distributed to the Panel prior to the meeting or if this is not possible to bring 40 copies to the meeting. Written statements can supplement and expand the oral presentation. Each speaker is asked to

provide contact information (name, affiliation, mailing address, phone, fax, email and sponsoring organization, if applicable) when registering to make oral comments.

Summary minutes and a final report of the Panel will be available following the meeting at the ICCVAM/NICEATM Web site (*http://iccvam.niehs.nih.gov*). ICCVAM will consider the conclusions and recommendations from the Panel and any public comments received in finalizing test method recommendations and performance standards for these test methods.

Background Information on ICCVAM and NICEATM

ICCVAM is an interagency committee composed of representatives from 15 U.S. 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 while refining (less pain and distress), reducing, and replacing animal use. The ICCVAM Authorization Act of 2000 (Pub. L. 106–545, available at *http://iccvam.niehs.nih.gov/about/PL106545.htm*) 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 U.S. Federal agencies. Additional information about ICCVAM and NICEATM can be found at the ICCVAM/NICEATM Web site: *http://iccvam.niehs.nih.gov.*

References

EPA. 2002a. Health Effects Test Guidelines OPPTS 870.1100 Acute Oral Toxicity. EPA 712–C–02–190. Washington, DC: U.S. Environmental Protection Agency.

ICCVAM. 2001a. Report of the international workshop on in vitro methods for assessing acute systemic toxicity. NIH Publication 01–4499. Research Triangle Park, NC: National Institute for Environmental Health Sciences. Available at: *http://iccvam.niehs.nih.gov/.*

ICCVAM. 2001b. Guidance document on using in vitro data to estimate in vivo starting doses for acute toxicity. NIH Publication 01–4500. Research Triangle Park, NC: National Institute for Environmental Health Sciences. Available at: *http://iccvam.niehs.nih.gov/.* OECD. 2001a. Guideline for Testing of Chemicals, 425, Acute Oral Toxicity—Up-and-Down Procedure. Paris France: OECD. Available at: *http://www.oecd.org* [accessed June 2, 2004]. OECD. 2001b. Guideline For Testing of Chemicals, 423, Acute Oral Toxicity—Acute Toxic Class Method. Paris France: OECD.

Dated: March 9, 2006.

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