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); Notice of Peer Review Meeting on the Revised Up-and-Down Procedure (UDP) as an Alternative Test Method for Assessing Acute Oral Toxicity; Request for Comments

Summary

Pursuant to Public Law 103–43, notice is hereby given of a public meeting coordinated by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and sponsored by NIEHS and the NTP. The agenda topic is the scientific peer review of the revised Up-and-Down Procedure, a method proposed as a replacement for the existing LD50 test for evaluating the acute oral toxicity potential of chemicals. The meeting will take place on July 25, 2000, from 8:30 a.m. to 5:30 p.m. at the Sheraton Crystal City Hotel, 1800 Jefferson Davis Highway, Arlington, VA 22202. The meeting is open to the public.

Background

ICCVAM, with participation by 14 Federal regulatory and research agencies and programs, was established in 1997 to coordinate issues relating to the development, validation, acceptance, and national/international harmonization of toxicological test methods. ICCVAM seeks to promote the scientific validation and regulatory acceptance of new and improved test methods applicable to Federal agencies including methods that may reduce and replace animal use, or that refine animal use to reduce or eliminate pain and distress. The Committee's functions include the coordination of interagency reviews of toxicological test methods and communication with stakeholders throughout the process of test method development and validation. The following Federal regulatory and research agencies and organizations participate in this effort:

Consumer Product Safety Commission
Department of Defense
Department of Energy
Department of Health and Human Services
  Agency for Toxic Substances and Disease Registry
  Food and Drug Administration
  National Institute for Occupational Safety and Health/CDC
  National Institutes of Health
  National Cancer Institute
  National Institute of Environmental Health Sciences
  National Library of Medicine
Department of the Interior
Department of Labor
  Occupational Safety and Health Administration
Department of Transportation
  Research and Special Programs Administration
Environmental Protection Agency

The NTP Center for the Evaluation of Alternative Toxicological Methods (NICEATM) was established in 1998 and provides operational support for the ICCVAM. NICEATM and ICCVAM seek to promote the validation and regulatory acceptance of new test methods that will enhance agencies' abilities to assess risks, and that will refine, reduce, and replace animal use. NICEATM and ICCVAM collaborate to carry out activities associated with the development, validation, and regulatory acceptance of proposed new and improved test methods. These activities may include:

Independent Peer Review Panel Meetings, which are typically convened following the completion of comprehensive validation studies on a test method. Independent peer review has been determined to be an essential prerequisite for consideration of a test method for regulatory acceptance. Peer Review Panels are asked to develop scientific consensus on the usefulness and limitations of test methods to generate information for specific human health and/or ecological risk assessment purposes. Following the independent peer review of a test method, ICCVAM forwards recommendations on their usefulness to agencies for their consideration. Federal agencies then determine the regulatory acceptability of a method according to their mandates.

Expert Panel Meetings, which are typically convened to evaluate the validation status of a method following the completion of initial development and pre-validation studies. An Expert Panel is asked to recommend additional validation studies that might be helpful in further characterizing the usefulness of a method and to identify any additional research and development efforts that might enhance the effectiveness of a method.

Test Method Workshops, which are convened, as needed, to evaluate the adequacy of current methods for assessing specific toxicities, to identify areas in need of improved or new testing methods, to identify research efforts that may be needed to develop new test methods, and to identify appropriate development and validation activities for proposed new methods.

Agenda

The agenda topic is the scientific peer review evaluation of the validation status of the revised Up-and-Down Procedure (UDP). This procedure is an updated version of the Organization for Economic Cooperation and Development (OECD) Test Guideline 425 (OECD Guideline for the Testing of Chemicals, Acute Oral Toxicity: Up-and-Down Procedure. Guideline 425, adopted September 21, 1998, OECD, Paris, France, *http://www.oecd.org/ehs/test*). The revised UDP is proposed as a substitute for the existing OECD Test Guideline 401 (OECD Guideline for the Testing of Chemicals, Acute Oral Toxicity, Guideline 401, adopted February 24, 1987, OECD, Paris, France). OECD has proposed that Guideline 401 should be deleted since three alternative methods are now available [OECD Document ENV/JM (99) 19, Test Guidelines Programme, Acute Oral Toxicity Testing: Data Needs and Animal Welfare Considerations, 29th Joint Meeting, June 8–11, 1999, Paris, France]. Prior to deletion of Guideline 401, U.S. agencies have requested that ICCVAM conduct an independent peer review of the revised UDP to determine the validity of the method as a substitute for Guideline 401. An Independent Peer Review Panel will (1) evaluate the extent to which 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://ntpserver.niehs.nih.gov/htdocs/ICCVAM/iccvam.html*) have been addressed, and (2) will provide conclusions and recommendations regarding the usefulness and limitations of the method as a substitute for the traditional acute oral toxicity test method (OECD Guideline 401, 1987). The UDP has the potential to reduce the number of animals required to classify chemicals for acute oral toxicity compared to Guideline 401. A request for nominations of expert scientists for the Panel was previously published (FR 65, 8385–8386, February 18, 2000).

The meeting will begin at 8:30 a.m. on July 25 and will conclude by 5 p.m. There will be a brief orientation on ICCVAM and the ICCVAM review process, followed by a peer review of the revised UDP and supporting

information. The Peer Review Panel will discuss the usefulness of the UDP as an alternative to the traditional LD50 methods currently accepted by government regulatory authorities for the assessment of acute oral toxicity potential of chemicals.

Background Document Available for Comment

NICEATM has prepared a Background Review Document that includes the revised UDP protocol and documents supporting the basis and validity of the test method. Copies of the Up-and-Down Procedure Background Review Document and supporting documentation may be obtained from NICEATM, MD EC–17, P.O. Box 12233, Research Triangle Park, NC, 27709, Phone: 919–541–3398, Fax: 919–541–0947, E-mail: *ICCVAM@niehs.nih.gov*. A copy of the Background Review Document and comments submitted will be available for viewing Monday through Friday, from 12 noon to 4 p.m. EST at the U. S. Environmental Protection Agency, Office of Prevention, Pesticides and Toxic Substances, Non-Confidential Information Center, Room 607B, Northeast Mall, 401 M Street, SW, Washington, DC 20460. Thirty days prior to the meeting, a detailed agenda will be available on the web at: *http://iccvam.niehs.nih.gov* or by contacting NICEATM.

Persons requesting additional information regarding the rationale for the OECD proposal to delete the OECD Guideline 401 can contact William T. Meyer, U.S. Environmental Protection Agency, Office of Pesticide Programs, Phone: 703–305–7188; E-mail: *Meyer,WilliamT@epa.gov*. Mail address: Ariel Rios Bldg., 1200 Pennsylvania Ave., NW, Mail Code 7506C, Washington, DC 20460; Federal Express address: 1921 Jefferson Davis Highway, Room 1104H, Arlington, VA 22202.

Request for Comments

NICEATM invites the submission of written comments on the revised Up-and-Down Procedure, and submission of other available information and data on the UDP, including information about completed, ongoing, or planned studies. Written comments and additional information should include name, affiliation, mailing address, phone, fax, e-mail and sponsoring organization (if any), and should be sent by mail, fax, or e-mail to NICEATM at the address listed above. Comments may be submitted anytime before the meeting; however, comments should be submitted by June 15 in order to ensure time for adequate review by the Panel. Written comments will be made available to the Peer Review Panel members, ICCVAM agency representatives and experts, and attendees at the meeting and will be included in the resource materials assembled on the UDP.

The Expert Panel Meeting will be open to the public, and time will be provided for presentation of public oral comments at designated times during the meeting. Speakers will be assigned on a first-come, first-serve basis and up to seven minutes will be allotted to each speaker. In order to facilitate planning, members of the public who wish to present oral statements at the meeting should contact NICEATM as soon as possible, but no later than July 18, 2000. Persons registering to make comments are asked to provide, if possible, a written copy of their statement in advance so that copies can be made and distributed to the Peer Review Panel members for their timely consideration prior to the meeting. Written statements can supplement and expand the oral presentation, and each speaker is asked to provide his/her name, affiliation, mailing address, phone, fax, e-mail and supporting organization (if any). Registration for making public comments will also be available on-site. If registering on-site to speak and reading oral comments from printed copy, the speaker is asked to bring 50 copies of the text. These copies will be distributed to the Panel and supplement the record.

Summary minutes from the meeting and the final report from the Peer Review Panel will be prepared and made available upon request to NICEATM (address provided above). These documents will also be made available via the internet at the website: *http://iccvam.niehs.nih.gov.*

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

Dated: May 22, 2000.

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