DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institute of Environmental Health Sciences (NIEHS); National Toxicology Program (NTP); The Revised Draft Up-and-Down Procedure for Assessing Acute Oral Toxicity: Notice of Availability and Request for Public Comments

Summary

Notice is hereby given of the availability of a revised draft Up-and-Down Procedure for assessing acute oral toxicity and solicitation of public comment. Documents available include: (1) A revised draft Up-and-Down Procedure (UDP) test guideline (hereafter, revised draft UDP); (2) A procedure incorporated into the revised draft UDP for calculating the confidence interval for the estimated median lethal dose (LD50); and (3) A software program for use in establishing test doses, determining when to stop the test, and estimating the LD50 and the confidence interval for the estimated LD50.

Availability of Revised Draft UDP Documents

The revised draft UDP was proposed by the U.S. Environmental Protection Agency (U.S. EPA) to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) as an alternate for the existing conventional LD50 test (EPA 870.1100) used to evaluate the acute oral toxicity of chemicals. A previous version of the draft UDP was reviewed by the UDP Peer Review Panel (hereafter, Panel) at a meeting on July 25, 2000 organized by the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and ICCVAM. This revised draft UDP incorporates modifications made in response to the conclusions and recommendations of the Panel and may be obtained electronically from the NICEATM/ICCVAM web site at http:/iccvam.niehs.nih.gov/methods/udpdocs/udprpt/udp_ciprop.htm. For a paper copy (a limited number are available), contact NICEATM at (919) 541–3398, or via e-mail at niceatm@niehs.nih.gov.

The proposed procedure for calculating the confidence interval for the estimated LD50 is a statistical calculation and does not require the use of test animals beyond what is needed to estimate the LD50. This procedure helps to place the estimated LD50 in a statistical context for hazard and risk assessment purposes. The confidence

interval procedure may be obtained electronically from the NICEATM/ICCVAM web site at http://iccvam.niehs.nih.gov/methods/udpdocs/udprpt/udp_ciprop.htm. For a paper copy (a limited number are available), contact NICEATM at (919) 541–3398, or via e-mail at niceatm@niehs.nih.gov. For technical clarification or questions regarding the confidence interval procedure, contact Dr. Amy Rispin, U.S. EPA, by telephone at (703) 305–5989 or via e-mail at rispin.amy@epa.gov.

Because the generation of parameters for this revised draft UDP is computationally intensive, the U.S. EPA developed a simple-to-use software program to aid in dose selection, test-stopping decisions, calculation of an estimate of the LD50, and calculation of a confidence interval around the LD50. The confidence interval procedure may be obtained electronically from the NICEATM/ICCVAM web site at http://iccvam.niehs.nih.gov/methods/udpdocs/udprpt/udp_ciprop.htm. To obtain a diskette of this software program, (a limited number are available), contact NICEATM at (919) 541–3398 or via e-mail at niceatm@niehs.nih.gov. For technical clarification or questions regarding the software package contact Dr. Elizabeth Margosches, U.S. EPA, by telephone at (202) 260–1511 or via e-mail at margosches.elizabeth@epa.gov, or Ms. Deborah McCall, U.S. EPA, by telephone at (703) 305–7109, or via e-mail at mccall.deborah@epa.gov.

Request for Public Comment

NICEATM invites written public comments on the revised draft UDP, the confidence interval proposal, and the software program. Comments should be sent to NICEATM through August 6, 2001. Comments submitted via e-mail are preferred; the acceptable file formats are MS Word (Office 98 or older), plain text, or PDF. Comments should be sent to Dr. William S. Stokes, Director, NICEATM, NIEHS, MD EC–17, P.O. Box 12233, Research Triangle Park, NC, 27709; telephone 919–541–2384; fax 919–541–0947; e-mail niceatm@niehs.nih.gov. Persons submitting written comments should include their contact information (name, affiliation, address, telephone and fax numbers, and e-mail) and sponsoring organization, if any. Public comments received in response to this **Federal Register** notice will be posted on the NICEATM/ICCVAM web site (http://iccvam.niehs.nih.gov). In addition, they will be available for viewing Monday through Friday, from noon to 4 p.m., excluding legal holidays, at the U.S. EPA under docket control number: AR–228, Up-and-Down Procedure. [U.S. EPA, Office of Prevention, Pesticides, and Toxic Substances, Non-Confidential Information Center, Room 607B, Northeast Mall, 401 M Street, SW., Washington, DC 20460, telephone: (202) 260–7099]. This docket also contains background and supporting materials for the revised draft UDP.

The comments will also be provided to the Panel for consideration in preparation for a final meeting tentatively planned for August 2001. This meeting is anticipated to be held as a teleconference with opportunity for public participation. An announcement of the Panel meeting with additional details will be published in a future **Federal Register** notice. The focus of this meeting will be to discuss the revised draft UDP, the proposed procedure for calculating the confidence interval for the estimated LD50, and the software program. Following the Panel meeting, a final report of the Panel's findings and recommendations will be published and made available to the public through NICEATM. In accordance with Public Law 106–545, ICCVAM will develop and forward test recommendations on the UDP to Federal agencies for their consideration. The ICCVAM recommendations will also be made available to the public.

Background

In 1999, the Organization for Economic Cooperation and Development (OECD) proposed deletion of its standard test guideline (TG) for assessing the acute oral toxicity of chemicals (TG 401; OECD, 1987). The rationale for deletion was that three alternative acute toxicity test methods had previously been adopted and could be used instead. Each method uses fewer animals than the procedure described in TG 401. One of these test methods is the UDP (OECD TG 425). Prior to formal deletion of TG 401, OECD determined that it was necessary to revise the three alternative methods to conform to the newly harmonized OECD hazard classification scheme (OECD, 1998). The U.S. EPA agreed to organize a Technical Task Force to revise the UDP (OECD TG 425). The revised UDP test method included two procedures different from the original UDP: a Limit Test for substances anticipated having minimal toxicity, and a Supplemental Test to determine the slope and confidence interval for the dose-response curve.

ICCVAM and NICEATM convened an international independent scientific peer review panel July 25, 2000, to evaluate the validation status of the revised UDP. The Panel concluded that the revised UDP Primary Test provided an improved estimate of acute oral toxicity with a reduction in the number of animals used compared to the existing conventional LD50 test (e.g., EPA 870.1100, TG 401). The Panel concluded that the proposed Limit Test procedure would be expected to perform as well as or better than the currently used EPA 870.1100 or TG 401 limit test for hazard classification, while using fewer animals. The Panel did not recommend the proposed UDP Supplemental Test procedure for use. Information on previous deliberations of the Panel can be found on the Internet at http://iccvam.niehs.nih.gov/udp.htm.

In recognition of the need for a procedure to calculate the confidence interval for the estimated median lethal dose determined using the UDP, the UDP Technical Task Force developed a procedure for use with UDP data from the primary procedure. As recommended by the Panel, the Supplemental Procedure has been deleted in the revised draft UDP and no further work on a procedure to generate dose-response slope information has been proposed. A specialized software program was subsequently developed by the U.S. EPA to facilitate implementation and use of the revised UDP.

Background for the UDP, including the availability of review materials, can be found in previous **Federal Register** notices (see FR Volume 65, Number 34, pages 8385–8386, February 18, 2000, and FR Volume 65, Number 106, pages 35109–35110, June 1, 2000). Minutes from the UDP Peer Review Panel meeting held July 25, 2000, may be found at http://iccvam.niehs.nih.gov/udp.htm.

Additional Information About ICCVAM and NICEATM

ICCVAM, with 15 participating Federal agencies, was established in 1997 to coordinate interagency issues on toxicological test method development, validation, regulatory acceptance, and national and international harmonization. The ICCVAM Authorization Act of 2000 (Pub. L. 106–545) formally authorized and designated ICCVAM as a permanent committee. The NICEATM was established in 1998 to collaborate with the ICCVAM to facilitate the development, scientific review, and validation of novel toxicological methods that predict human health risks while reducing, refining, and/or replacing animal tests and to promote communication with stakeholders. The NICEATM is located at the NIEHS in Research Triangle Park, NC. Additional information concerning ICCVAM and NICEATM can be found

on the ICCVAM/NICEATM web site at http://iccvam.niehs.nih.gov.

References

U.S. EPA (1998). Health Effects Test Guidelines, OPPTS 870.1100, Acute Oral Toxicity. Washington, DC: U.S. Environmental Protection Agency, 1998. Available on the Internet at http://www.epa.gov/docs/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/.

OECD (1987). TG 401. OECD Guideline for the Testing of Chemicals, Acute Oral Toxicity, Adopted February 24, 1987, OECD, Paris, France.

OECD (1998). Harmonized Integrated Hazard Classification System for Human Health and Environmental Effects of Chemical Substances as endorsed by the 28th Joint Meeting of the Chemicals Committee and Working Party on Chemicals in November 1998. Available on the Internet at http://www.oecd.org/ehs/Class/HCL6.htm.

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Samuel H. Wilson,

Deputy Director, National Institute of Environmental Health Sciences.

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