DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institute of Environmental Health Sciences (NIEHS); National Toxicology Program (NTP); Report on the Revised Up-and-Down Procedure: A Test Method for Determining the Acute Oral Toxicity of Chemicals; Notice of Availability and Request for Public Comments

SUMMARY: Notice is hereby given of the availability of the report entitled, ''The Revised Up-and-Down Procedure: A

Test Method for Determining the Acute Oral Toxicity of Chemicals,'' NIH Publication 02–4501. The report contains the final test recommendations on the '' Revised Up-and-Down Procedure'' (Revised UDP) by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), the results of an independent scientific peer review evaluation of the Revised UDP, and the final test guideline for the Revised UDP. The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) is seeking public comment on this report on behalf of the ICCVAM prior to transmittal to US Federal agencies in accordance with Pub. L. 106–545. The report and public comments will be transmitted to appropriate Federal agencies following this public comment period.

Availability of the Report

The report is available electronically (PDF and HTML) on the ICCVAM/NICEATM Web site, *http://iccvam.niehs.nih.gov.* A limited number of printed reports are available. To receive a printed copy, please contact NICEATM at PO Box 12233, MD EC–17, Research Triangle Park, NC 27709 (mail), 919–541–2384 (phone), 919–541–0947 (fax), or *niceatm@niehs.nih.gov* (e-mail).

Request for Public Comments

NICEATM invites written public comments on the report. Comments should be sent to NICEATM no later than March 25, 2002. 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, at PO Box 12233, MD EC–17, Research Triangle Park, NC 27709 (mail), 919–541–0947 (fax), or *niceatmcomments@niehs.nih.gov* (e-mail). 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 by the above deadline will be posted on the ICCVAM/NICEATM Web site, *http://iccvam.niehs.nih.gov*, and forwarded to the appropriate Federal agencies with the report.

Background

The Organisation for Economic Cooperation and Development (OECD) Test Guidelines Program (TG 425; OECD 1998) adopted the UDP in 1998. The U.S. Environmental Protection Agency (EPA) subsequently determined it was necessary to revise the UDP to: (1) Conform to a newly harmonized global hazard classification scheme for acute toxicity (OECD, 2001) and (2) ensure that regulatory and testing needs would be met with the Revised UDP prior to OECD's proposed deletion of the conventional acute oral toxicity test (OECD, 1987). In August 1999, the EPA asked ICCVAM to evaluate the validation status of the Revised UDP as a substitute for the existing conventional LD50 test (U.S. EPA 870.1100, 1998; OECD Test Guideline (TG) 401, 1987).

The Revised UDP test method submitted to ICCVAM for evaluation included three components:

- A Primary Test for estimating the median lethal dose using sequential testing.
- A Limit Test for evaluating substances anticipated to have minimal or no toxicity.
- A Supplemental Test to determine the slope and confidence interval (CI) for the dose-response curve.

An initial **Federal Register** notice (Vol. 65, No. 34, pp. 8385–8386, February 18, 2000) requested data and the nomination of expert scientists to participate in the independent scientific peer review evaluation of the Revised UDP. A second **Federal Register** notice (Vol. 65, No. 106, pp. 35109–35110, June 1, 2000) announced the peer review panel meeting, availability of a background review document on the Revised UDP, and requested public comments.

The first meeting of the Panel to evaluate the Revised UDP was held on July 25, 2000. The public meeting was organized by the ICCVAM and NICEATM and was sponsored by the NIEHS, NTP, and EPA. The Panel evaluated the extent to which the Revised UDP addresses established validation and acceptance criteria (ICCVAM, 1997) and developes conclusions regarding the usefulness and limitations of the Revised UDP.

The Panel agreed that the Primary and Limit tests would perform as good or better than the respective existing conventional LD50 and limit tests. They also agreed that the revised test methods would reduce animal use compared to the current test methods. The Panel provided other recommendations for revision of the Revised UDP test guideline and did not recommend the UDP Supplemental Test.

Based on the Panel's July 25, 2000 conclusions and recommendations, the EPA UDP Technical Task Force modified the UDP Primary and Limit Tests and removed the UDP Supplemental Test. A computational procedure was added to calculate the confidence interval (CI) for the estimated LD50. The EPA also developed a software program that would calculate subsequent test doses, determine when to stop the test, estimate the LD50, and calculate a CI for the LD50. The publicly available software was developed to mitigate complexity for the user and to facilitate correct performance of the Revised UDP.

A **Federal Register** notice (Vol. 66, No. 121, pp. 33550–33552, June 22, 2001) requested public comment and announced availability of the revised draft test guideline for the Revised UDP, the procedure for calculating the confidence interval for the estimated LD50, and the software program. A subsequent **Federal Register** notice (Vol. 66, No. 133, pp. 36294–36295, July 11, 2001) announced a second public meeting of the UDP Panel.

The second meeting of the UDP Panel was held by teleconference on August 21, 2001. The Panel reviewed and endorsed modifications to the Revised UDP, the CI procedure, and the software program. The Panel recommended additional clarifications to the Revised UDP. Written reports of the Panel meetings are included in the final report.

Following the August 21st meeting, the EPA UDP Technical Task Force revised the UDP Guideline in response to the Panel's recommendations. A discussion of software program limitations and information about using *in vitro* cytotoxicity data to estimate starting doses for *in vivo* studies were added. An ICCVAM Acute Toxicity Working Group and the ICCVAM reviewed and endorsed the final Revised UDP Test Guideline, and developed and adopted ICCVAM test method recommendations for the Revised UDP. In accordance with P.L. 106–545, the ICCVAM test recommendations will be forwarded to appropriate Federal agencies for acceptance consideration.

The final report comprises two volumes. The first volume (143 pages) includes the final ICCVAM test method recommendations on the Revised UDP procedure, the final Revised UDP Test Guideline, and the two peer review panel meeting reports. Volume 2 (291 pages) contains an updated background review document and other information considered by the Panel for the July 2000 meeting. Following receipt of public comments, the report will be forwarded to Federal agencies in accordance with Pub. L. 106–545.

Additional Information About ICCVAM and NICEATM

The NICEATM and ICCVAM were established to facilitate development, validation, and regulatory acceptance of improved toxicological methods that predict human health risks while reducing, refining, and/or replacing animal tests and to promote communication with stakeholders. The NICEATM coordinates activities for the ICCVAM and is located at the NIEHS, Research Triangle Park, NC. ICCVAM, with 15 participating Federal agencies, originally established in 1997, was formally authorized and designated as a permanent interagency coordinating committee by the ICCVAM Authorization Act of 2000 (Pub. L. 106–545). ICCVAM's duties include the technical evaluation of new and alternative testing methods, the development of test recommendations based on those technical evaluations, and the forwarding of its test recommendations to Federal agencies for their consideration. The ICCVAM also coordinates interagency issues on toxicological test method development, validation, regulatory acceptance, and national and international harmonization. Additional information about ICCVAM and NICEATM can be found on the ICCVAM/NICEATM Web site at *http://iccvam.niehs.nih.gov.*

References

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National Institute of Environmental Health Sciences (NIEHS). 2000a. National Toxicology Program: Request for Data and Nomination of Expert Scientists to Participate in the Independent Peer Review Evaluation of the Revised Up-and-Down Procedure for Assessing Acute Oral Toxicity. Evaluation of the Up-and-Down Procedure. 65 FR 8385. February 18, 2000.

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