DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Toxicology Program (NTP); NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Availability of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Test Method Evaluation Report: In Vitro Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Tests and the Final Background Review Document for In Vitro Cytotoxicity Test Methods for Estimating Acute Oral Systemic Toxicity; Notice of Transmittal of ICCVAM Test Method Recommendations to Federal Agencies

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

ACTION: Availability of ICCVAM Test Method Evaluation Report and Final Background Review Document.

SUMMARY: NICEATM announces availability of the *ICCVAM Test Method Evaluation Report: In Vitro Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Tests* (NIH Publication 07–4519). The report describes two *in vitro* basal cytotoxicity neutral red uptake (NRU) test methods that can be used for estimating starting doses for acute oral toxicity tests. The report includes ICCVAM's (a) final test method recommendations on the use of these two test methods, (b) recommended test method protocols for future use, (c) recommendations for future studies to further characterize the usefulness and limitations of *in vitro* methods for assessing acute systemic toxicity, and (d) recommended performance standards for tests with similar scientific principles and that measure or predict acute oral systemic toxicity. The report recommends the use of these methods in a weight-of-evidence approach to determine starting doses for acute oral systemic toxicity tests with rodents. The report also recommends that these *in vitro* test methods be considered before using animals for acute oral systemic toxicity testing and used when determined appropriate.

NICEATM also announces the availability of the final *Background Review Document: In Vitro Cytotoxicity Test Methods for Estimating Acute Oral Systemic Toxicity* (BRD) (NIH Publication 07–4518). The BRD provides data and analyses from a collaborative international validation study organized by NICEATM and the European Centre for the Validation of Alternative Methods (ECVAM) to evaluate the usefulness and limitations of two *in vitro* basal cytotoxicity NRU test methods using either BALB/c 3T3 mouse fibroblasts (3T3) or primary human epidermal keratinocytes (NHK) for estimating acute oral rodent toxicity.

Electronic copies of the ICCVAM Test Method Evaluation Report and the BRD are available from the ICCVAM/NICEATM Web site at *http://iccvam.niehs.nih.gov* or by contacting NICEATM (see **FOR FURTHER INFORMATION CONTACT**). The ICCVAM Test Method Evaluation Report and the final BRD have been forwarded to U.S. Federal agencies for regulatory and other acceptance considerations where applicable. Responses will be posted on the ICCVAM/NICEATM Web site as they are received.

FOR FURTHER INFORMATION CONTACT: Dr. William S. Stokes, Director, NICEATM, 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, NIEHS, 79 T.W. Alexander Drive, Building 4401, Room 3128, Research Triangle Park, NC 27709.

SUPPLEMENTARY INFORMATION:

Background

In 2002, NICEATM and ECVAM initiated a collaborative, international, multi-laboratory validation study to independently evaluate the usefulness of the 3T3 and NHK NRU basal cytotoxicity test methods for estimating acute oral rodent toxicity and for estimating starting doses for *in vivo* rodent acute oral toxicity tests. The 3T3 and NHK NRU test methods were evaluated with 72 reference substances. Once the study was completed in January 2005, NICEATM prepared a draft BRD that contained comprehensive summaries of the data generated in the validation study, analyses of the relevance and reliability of the two test methods, and simulation analyses of the refinement (i.e., to lessen or avoid pain and distress) and reduction in animal use that might occur if these tests were used as adjuncts to two acute oral toxicity test methods (i.e., the Up-and-Down Procedure and the Acute Toxic Class method). The draft BRD was released for public comment on March 21, 2006 (**Federal Register**, Vol. 71, No. 54, pp. 14229–14231).

On May 23, 2006, NICEATM, on behalf of ICCVAM, convened an independent, scientific peer review panel meeting to review the draft BRD and evaluate the validation status of the 3T3 and NHK NRU test methods for determining starting doses for *in vivo* acute oral systemic toxicity tests. The peer review panel's report was released in July 2006 (**Federal Register**, Vol. 71, No. 132, pp. 39122–39123). At a public teleconference meeting on August 3, 2006 (**Federal Register**, Vol. 71, No. 132, pp. 39121–39122), the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) reviewed and endorsed the conclusions of the peer review panel (minutes from the teleconference are available at *http://ntp.niehs.nih.gov/files/SACATMAug06MinutesVF081506.pdf*).

ICCVAM considered the peer panel report, public comments, SACATM comments, and the draft BRD in finalizing its recommendations on the use of these two *in vitro* basal cytotoxicity test methods for estimating starting doses for acute oral systemic toxicity tests. The ICCVAM Test Method Evaluation Report includes the ICCVAM

recommendations on the use of the two *in vitro* NRU test methods, as well as recommended test method protocols, recommendations for future studies to further characterize the usefulness and limitations of *in vitro* methods for assessing acute systemic toxicity, recommended performance standards for tests with similar scientific principles and that measure or predict acute oral systemic toxicity, the peer panel report and **Federal Register** notices. The final BRD, which provides the supporting documentation for this report, is available as a separate document. The ICCVAM Test Method Evaluation Report and the supporting final BRD were forwarded to U.S. Federal agencies for their consideration for regulatory acceptance as required by the ICCVAM Authorization Act of 2000 (42 U.S.C. 285*l*–3). Agencies' responses to the test method recommendations will be posted on the ICCVAM/NICEATM Web site as they are received.

Background Information on ICCVAM, NICEATM, and SACATM

ICCVAM is an interagency committee composed of representatives from 15 Federal regulatory and research agencies that use, generate, or disseminate 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, and replace animal use. The ICCVAM Authorization Act of 2000 established ICCVAM as a permanent interagency committee of the NIEHS under NICEATM. NICEATM administers 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 on their Web site (*http://iccvam.niehs.nih.gov*).

SACATM was established January 9, 2002, and is composed of scientists from the public and private sectors (**Federal Register**, Vol. 67, No. 49, page 11358). SACATM provides advice to the Director of the NIEHS, to ICCVAM, and to NICEATM regarding the 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'' (or directly at *http://ntp.niehs.nih.gov/go/167*).

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