DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Toxicology Program (NTP), NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Availability of Peer Review Panel Report on the Use of *In Vitro* Basal Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Testing and Request for Comments

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

ACTION: Request for comments.

SUMMARY: The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), in collaboration with the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), organized an independent, scientific peer review meeting on May 23, 2006, to evaluate the validation status of the *in vitro* 3T3 and normal human keratinocyte (NHK) neutral red uptake (NRU) basal cytotoxicity test methods. These two *in vitro* cytotoxicity test methods are proposed as adjuncts (for the purpose of determining the starting dose) to *in vivo* acute oral toxicity tests. The peer review report from this meeting, entitled *Peer Review Panel Evaluation of the Use of In Vitro Basal Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Testing*, is now available. The report contains (1) a summary of the peer review evaluation and (2) the peer review panel's (Panel) conclusions on the draft ICCVAM test method recommendations regarding the proposed usefulness, limitations, and validation status of the 3T3 and NHK cytotoxicity test methods. The NICEATM invites public comment on the Panel's conclusions on the draft ICCVAM test method recommendations. Copies of the Panel report may be obtained on the ICCVAM/NICEATM Web site at *http://iccvam.niehs.nih.gov*, or by contacting NICEATM at the address given below.

DATES: Written comments should be received at NICEATM by August 25, 2006.

ADDRESSES: Public comments and any other correspondence should be sent by mail, fax, or e-mail to Dr. William S. Stokes, 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.

SUPPLEMENTARY INFORMATION:

Background

The 3T3 and NHK cytotoxicity test methods are proposed as adjuncts (for the purpose of determining the starting dose) to *in vivo* acute oral toxicity test methods (*i.e.*, the Up-and-Down Procedure [EPA 2002a; OECD 2001a], the Acute Toxic Class method [OECD 2001b]) to refine (*i.e.*, to lessen or avoid pain and distress) and/or reduce animal use. Both *in vitro* cytotoxicity test methods have been assessed in a NICEATM and European Centre on the Validation of Alternative Methods (ECVAM) collaborative independent validation study. At this peer review meeting, the Panel reviewed the background review document (BRD) on the 3T3 and NHK cytotoxicity test methods and evaluated the extent that established validation and acceptance criteria had been adequately addressed for the intended purpose of the test methods. The Panel also provided comments on draft ICCVAM recommendations regarding the proposed use of these test methods, draft test method protocols, draft performance standards, and draft recommended future studies. The Panel's conclusions and recommendations on the two *in vitro* cytotoxicity test methods are described in the *Peer Review Panel Evaluation of the Use of In Vitro Basal Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Testing* (available at *http://iccvam.niehs.nih.gov/*).

Prior to the Panel meeting, NICEATM issued **Federal Register** notices to (1) recommend that in vitro basal cytotoxicity test methods be considered as tools for estimating starting doses for in vivo acute systemic toxicity tests (66FR49686), (2) announce a request for nominations for Panel members and submission of existing in vivo and in vitro data (70FR14473), (3) announce the independent peer review meeting on the use of the 3T3 and NHK cytotoxicity test methods for estimating starting doses for acute oral systemic toxicity tests, and (4) request comments on the draft BRD and draft ICCVAM recommendations (71FR14229). All **Federal Register** notices, the draft BRD, and the draft ICCVAM recommendations are available at *http://iccvam.niehs.nih.gov/*.

Request for Comments

NICEATM invites the submission of written comments on the Panel's

conclusions on the draft ICCVAM test method recommendations. When submitting written comments please refer to this **Federal Register** notice and include appropriate contact information (name, affiliation, mailing address, phone, fax, e-mail and sponsoring organization, if applicable). All comments received by the deadline listed above will be placed on the ICCVAM/NICEATM Web site and made available to ICCVAM. In addition, there will be an opportunity for oral public comments on the draft ICCVAM test method recommendations for the 3T3 and NHK cytotoxicity test methods during a teleconference meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) scheduled for August 3, 2006. Details of the SACATM teleconference are published as a separate **Federal Register** notice (available at *http://ntp.niehs.nih.gov/go/frn*). Any written comments on the Panel report received prior to July 25, 2006, will be distributed to SACATM.

ICCVAM will consider the Panel report along with SACATM and public comments received on that report as it prepares final ICCVAM recommendations for the 3T3 and NHK cytotoxicity test methods. An ICCVAM test method evaluation report, which will include the final ICCVAM recommendations, will be forwarded to the appropriate federal agencies for their consideration. This report also will be available to the public on the ICCVAM/NICEATM website and by request from NICEATM.

Background Information on ICCVAM, NICEATM, and SACATM

ICCVAM is an interagency committee composed of representatives from 15 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 and that refine, reduce, or replace animal use. The ICCVAM Authorization Act of 2000 [42 U.S.C. 285l-3(d)] establishes 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 Federal agencies. Additional information about ICCVAM and NICEATM can be found at the ICCVAM-NICEATM Web site (*http://iccvam.niehs.nih.gov*).

SACATM was established January 9, 2002, to fulfill section 3(d) of the ICCVAM Authorization Act of 2000 and is composed of scientists from the public and private sectors (**Federal Register**: March 13, 2002: Vol. 67, No. 49, page 11358). SACATM provides advice to the Director of the NIEHS, ICCVAM, and NICEATM regarding 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/go/167*.

References

EPA. 2002. Health Effects Test Guidelines OPPT 870.1100 Acute Oral Toxicity. EPA 712–C–02–190. Washington, DC: U.S. Environmental Protection Agency. Available at: *http://www.epa.gov/opptsfrs/publications/*.

ICCVAM. 2003. ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods. NIH Publication No. 03–4508. Research Triangle Park, NC: NIEHS. 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*.

OECD. 2001b. Guideline for Testing of Chemicals, 423, Acute Oral Toxicity—Acute Toxic Class Method. Paris, France:OECD. Available at: *http://www.oecd.org*.

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