

valid for use as replacements for the animal test and were ready to be considered for regulatory acceptance (Balls and Corcelle, 1998; Balls and Hellsten, 2000). The European Scientific Committee for Cosmetic Products and Non-food Products (SCCNFP) evaluated the EPISKIN™ and Rat Skin TER and concluded that they were applicable for the safety evaluation of cosmetic ingredients or mixtures of ingredients (Anon., 1999). The European Commission subsequently adopted EpiDerm™, EPISKIN™, and Rat Skin TER (Anon., 2000).

#### Proposed ICCVAM Recommendations

ICCVAM proposes that these assays can be used to assess the dermal corrosion potential of chemicals in a weight-of-evidence approach in an integrated testing scheme [e.g., OECD Globally Harmonised Classification System (OECD, 1998); OECD Revised Proposals for Updated Test Guidelines 404 and 405: Dermal and Eye Corrosion/Irritation Studies (OECD, 2001a)]. These integrated testing schemes for dermal irritation/corrosion allow for the use of validated and accepted *in vitro* methods. In this approach, positive *in vitro* corrosivity responses do not generally require further testing and can be used for classification and labeling. Negative *in vitro* corrosivity responses shall be followed by *in vivo* dermal corrosion/irritation testing. (Note: The first animal used in the irritation/corrosivity assessment would be expected to identify any chemical corrosives that were false negatives in the *in vitro* test). Furthermore, as is appropriate for any *in vitro* assay, there is the opportunity for confirmatory testing if false positive results are indicated on a weight of evidence evaluation of supplemental information, such as pH, structure activity relationships (SAR), and other chemical and testing information.

#### 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 (Public Law 106–545) formally authorized and designated ICCVAM as a permanent committee administered by the NIEHS with specific duties that include the technical evaluation of new and alternative testing methods. ICCVAM is charged with developing test recommendations based on those

technical evaluations, and forwarding these to Federal agencies for their consideration. The NICEATM was established in 1998 to coordinate and facilitate ICCVAM activities, to provide peer review for validation activities and to promote communication with stakeholders. The NICEATM is located at the NIEHS, 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>.

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Dated: September 21, 2001.

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## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Public Health Service

#### National Institute of Environmental Health Sciences (NIEHS); National Toxicology Program (NTP)

Report of the International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity; Guidance Document on Using *In Vitro* Data to Estimate *In Vivo* Starting Doses for Acute Toxicity; Notice of Availability and Request for Public Comment.

#### Summary

Notice is hereby given of the availability of the reports entitled, "Report of the International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity" NIH Publication 01–4499 and "Guidance Document on Using *In Vitro* Data to Estimate *In Vivo* Starting Doses for Acute Toxicity" NIH Publication 01–4500. The Report provides conclusions and recommendations from expert scientists based on their review of current *in vitro* methods for assessing acute toxicity at an October 17–20, 2000 workshop. The workshop was organized by the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). The Guidance Document

provides Standard Operating Procedures (SOPs) for performing two in vitro basal cytotoxicity assays and describes how to use this in vitro data to predict starting doses for in vivo acute oral toxicity studies.

#### Availability of the Documents

To receive a copy of either report, please contact NICEATM at P.O. Box 12233, MD EC-17, Research Triangle Park, NC 27709 (mail), 919-541-3398 (phone), 919-541-0947 (fax), or [niceatm@niehs.nih.gov](mailto:niceatm@niehs.nih.gov) (email). The reports are also available on the ICCVAM/NICEATM website at <http://iccvam.niehs.nih.gov>.

#### Request for Public Comments

NICEATM invites written public comments on the Workshop Report and the Guidance Document. Comments should be sent to NICEATM by November 13, 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, PO Box 12233, Research Triangle Park, NC, 27709; telephone 919-541-2384; fax 919-541-0947; e-mail [niceatm@niehs.nih.gov](mailto: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>).

#### Background

The International Workshop on In Vitro Methods for Assessing Acute Systemic Toxicity was held October 17-20, 2000, at the Hyatt Regency Crystal City Hotel, 2799 Jefferson Davis Highway, Arlington, VA 22202. The workshop was organized by the NICEATM and ICCVAM, and sponsored by the NIEHS, the NTP, and U.S. EPA. The objectives of the workshop were (1) to assess the current validation status of in vitro test methods that might be useful for assessing the acute systemic toxicity potential of chemicals and (2) to develop recommendations for future research, development, and validation studies that might further enhance the use of in vitro methods for this purpose.

A **Federal Register** notice (Vol. 65, No. 115, pp. 37400-37403, June 14, 2000) requested information and data that should be considered at the workshop, and nominations of expert scientists to participate in the workshop. A second **Federal Register**

notice (Vol. 65, No. 184, pp. 57203-57205, September 21, 2000) announced availability of the workshop agenda, registration information, and a background summary of available in vitro methods.

At the workshop, the invited expert scientists were divided into four breakout groups as follows:

- Breakout Group 1: In Vitro Screening Methods for Assessing Acute Toxicity
- Breakout Group 2: In Vitro Methods for Toxicokinetic Determinations
- Breakout Group 3: In Vitro Methods for Predicting Organ-Specific Toxicity
- Breakout Group 4: Chemical Data Sets for Validation of In Vitro Acute Toxicity Test Methods

Each breakout group subsequently prepared a written report that represented the consensus of the invited scientists assigned to that group and these reports are included in the Workshop Report. It also includes as appendices: A detailed workshop agenda; summary minutes of plenary sessions and public comments; the background document for workshop participants; a NICEATM summary of the Multicenter Evaluation of In Vitro Cytotoxicity (MEIC); a summary of Federal regulations on acute toxicity; related **Federal Register** notices; and ICCVAM test method recommendations. The ICCVAM test recommendations were developed following the workshop to forward to Federal agencies in accordance with Pub. L. 106-545.

The Breakout Group on In Vitro Screening Methods recommended preparation of a document that would provide guidance on how to use in vitro data to estimate starting doses for in vivo acute toxicity studies. Three scientists subsequently collaborated with the NICEATM to develop a "Guidance Document on Using In Vitro Data to Estimate In Vivo Starting Doses for Acute Toxicity". The Guidance Document provides SOPs for conducting two in vitro cytotoxicity tests (the BALB/c 3T3 Neutral Red Uptake (NRU) and the Normal Human Keratinocyte (NHK) NRU assays) and instruction for using these assays to estimate starting doses for in vivo testing. The Guidance Document also includes the ZEBET (German National Centre for the Documentation and Evaluation of Alternatives to Animal Experimentation) Registry of Cytotoxicity (RC) Regression Analysis that provides a mathematical relationship between acute oral systemic rodent toxicity and in vitro basal cytotoxicity using data for 347 chemicals (Halle, 1998; Spielmann et al., 1999). The Guidance Document

expands on an approach suggested by Spielmann and colleagues that—as an initial step—the relationship found with the RC data be used to predict starting doses for subsequent in vivo acute lethality assays.

#### 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 administered by the NIEHS with specific duties that include the technical evaluation of new and alternative testing methods. ICCVAM is charged with developing test recommendations based on those technical evaluations, and forwarding these to Federal agencies for their consideration. The NICEATM was established in 1998 to coordinate and facilitate ICCVAM activities, to provide peer review for validation activities and to promote communication with stakeholders. The NICEATM is located at the NIEHS, 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>. In accordance with Public Law 106-545, the Workshop Report and the Guidance Document will be forwarded with ICCVAM test recommendations to Federal agencies for their consideration.

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Dated: September 18, 2001.

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