Health, 6701 Rockledge Drive, Room 3190, MSC 7848, Bethesda, MD 20892, (301) 435–1507.

Name of Committee: Center for Scientific Review Special Emphasis Panel.

Date: October 11, 2001.

Time: 9:00 am to 5:00 pm.

Agenda: To review and evaluate grant applications.

Place: Holiday Inn, 8120 Wisconsin Avenue, Bethesda, MD 20814.

Contact Person: Richard Marcus, PhD, Scientific Review Administrator, Center for Scientific Review, National Institutes of Health, 6701 Rockledge Drive, Room 5168, MSC 7844, Bethesda, MD 20892, (301) 435–1245, richard.marcus.@nih.gov.

Name of Committee: Center for Scientific Review Special Emphasis Panel.

Date: October 11, 2001.

Time: 1:00 pm to 2:30 pm.

Agenda: To review and evaluate grant applications.

Place: NIH, Rockledge 2, Bethesda, MD 20892, (Telephone Conference Call).

Contact Person: Victor A. Fung, PhD, Scientific Review Administrator, Center for Scientific Review, National Institutes of Health, 6701 Rockledge Drive, Room 4120, MSC 7804, Bethesda, MD 20814–9692, (301) 435–3504, fungv@csr.nih.gov.

(Catalogue of Federal Domestic Assistance Program Nos. 93.306, Comparative Medicine, 93.306; 93.333, Clinical Research, 93.333, 93.337, 93.393–93.396, 93.837–93.844, 93.846–93.878, 93.892, 93.893, National Institutes of Health, HHS)

Dated: September 20, 2001.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

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

EPISKIN™, EpiDerm™, and Rat Skin Transcutaneous Electrical Resistance Methods: In Vitro Test Methods Proposed for Assessing the Dermal Corrosivity Potential of Chemicals; Notice of Availability of a Background Review Document and Proposed ICCVAM Test Method Recommendations and Request for Public Comment.

Summary

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) announces availability of a background review document (BRD) entitled ''EPISKIN™, EpiDerm™, and Rat Skin Transcutaneous Electrical Resistance (TER) Methods: In Vitro Test Methods for Assessing the Dermal Corrosivity Potential of Chemicals,'' and proposed test method recommendations from the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) on the use of these methods. The NICEATM invites public comment on the BRD and ICCVAM recommendations.

Availability of Background Review Document and Proposed ICCVAM Recommendations

An electronic version of this BRD and proposed ICCVAM test method recommendations may be obtained from the NICEATM/ICCVAM web site at *http://iccvam.niehs.nih.gov*. For a paper copy (a limited number are available), please contact the NICEATM at (919) 541–3398 or via email at *niceatm@niehs.nih.gov*.

Request for Public Comment

NICEATM invites written public comments on the BRD on in vitro corrosivity methods and the proposed ICCVAM recommendations for these methods. The deadline for submission of comments is November 13, 2001. Comments submitted via email are preferred; the acceptable file formats are MS Word (Office 98 or older), plain text, or PDF. Comments should be sent to Dr. William Stokes, Director, NICEATM, NIEHS, MD EC–17, P.O. Box 12233, Research Triangle Park, NC, 27709; telephone 919–541–3398; fax 919–541–0947; email *niceatm@niehs.nih.gov*. Persons submitting written comments should include their contact information (name, affiliation, address, telephone/fax numbers, and email) 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* and provided to the ICCVAM. ICCVAM will consider all comments prior to finalizing its test recommendations on EpiDerm™, EPISKIN™, and Rat Skin TER. In accordance with Public Law 106–545, ICCVAM test recommendations will be forwarded to appropriate Federal agencies and will be made available to the public on the NICEATM/ICCVAM website.

Background

ICCVAM and the ICCVAM Corrosivity Working Group (CWG) recently evaluated three in vitro test methods for assessing the dermal corrosivity potential of chemicals and chemical mixtures—EpiDerm™, EPISKIN™, and Rat Skin TER. EpiDerm™ and EPISKIN™ utilize a three dimensional human skin model comprised of a reconstructed epidermis and a functional stratum corneum. The test chemical is applied to this reconstructed epidenmis for a specified time and subsequent cell viability is measured. Rat Skin TER assesses the skin corrosivity of a chemical by applying the test material to the epidermal surface of a rat skin disc for two and 24 hours; subsequently, the transcutaneous electrical resistance (TER) of the skin disc is measured. NICEATM prepared a background review document summarizing the available data and prior reviews for the three test methods, which was then considered by the CWG and ICCVAM. The CWG concluded, based on the information provided and outcomes of the previous reviews, that further evaluation by an independent scientific peer review panel did not appear necessary, and recommended that these methods undergo ICCVAM evaluation using an expedited review process (ICCVAM, 2001). ICCVAM agreed with the CWG recommendation for expedited review. This process involves the development of a draft ICCVAM position (proposed ICCVAM test recommendations) and publishing the position in the **Federal Register** for public comment. Public comments are considered by ICCVAM, and if no major problems are found, ICCVAM then finalizes its test recommendations and forwards to federal agencies for their determination of regulatory acceptability. If major problems are noted, then ICCVAM will determine an appropriate process for further evaluation, such as an independent peer review panel evaluation.

ECVAM Evaluation

The European Center for the Validation of Alternative Methods (ECVAM) conducted validation studies on these three in vitro methods (Barratt et al., 1998; Fentem et al., 1998; Liebsch et al., 2000). The ECVAM Management Team concluded that EpiDerm™, Rat Skin TER, and EPISKIN™ were scientifically valid for use as replacements for the animal test currently used to distinguish between corrosive and non-corrosive chemicals and for all chemical classes (Fentem et al., 1998; Liebsch et al., 2000).

Other Reviews

The validation status of these three methods was then evaluated by the ECVAM Scientific Advisory Committee (ESAC). The ESAC also concluded that the Rat Skin TER, EpiDerm™, and the EPISKIN™ tests were scientifically

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*.

References

Anon. EU Commission Directive 2000/33/EC of 25 April 2000 (Official Journal of the European Communities), Skin Corrosion, Rat Skin TER and Human Skin Model Assay. OJ L 136, June 8, 2000. Available: *http://embryo.ib.amwaw.edu.pl/invittox/prot/1_13620000608en00010089.pdf* [cited July 19, 2001].

Anon. Scientific Committee for Cosmetic Products, and Non-food Products intended for Consumers. Excerpts of the Outcome of Discussions Record of the 6th Plenary Meeting (SCCNFP) Brussels, Belgium. January 20, 1999. Available: *http://europa.eu.int/comm/food/fs/sc/sccp/out50_en.html* [cited July 19, 2001].

Balls M, Corcelle G. ''Statement on the scientific validity of the Rat Skin Transcutaneous Electrical Resistance (TER) Test (an in vitro test for skin corrosivity) and Statement of the scientific validity of the EPISKIN™ test (an in vitro test for skin corrosivity),'' dated April 3, 1998. Statement from the European Commission Joint Research Centre, Environment Institute, Ispra (VA), Italy presenting the results of the 10th ECVAM Scientific Advisory Committee (ESAC) meeting on March 31 (1998). Available: *http://www.iivs.org/news/ratskin-episkin.html* [cited July 19, 2001].

Balls M, Hellsten E. ''Statement on the application of the EpiDerm™ human skin model for corrosivity testing,'' dated March 20, 2000. ECVAM Scientific Advisory Committee meeting, Ispra, Italy, March 14–15 (2000).

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Organization for Economic Co-operation and Development (OECD). 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 the Working Party on Chemicals, OECD, Paris, France. (November 1998) *http://www.oecd.org/ehs/Class/HCL6.htm*

OECD. OECD Revised Proposals for Updated Test Guidelines 404 and 405: Dermal and Eye Corrosion/Irritation Studies. [OECD ENV/JM/TG (2001)2]. OECD Environment Directorate, Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. Test Guidelines Programme. Circulated in preparation for the 13th Meeting of the Working Group of the National Coordinators of the Test Guidelines Programme, OECD, Paris, France. (2001a)

Dated: September 21, 2001.

Samuel H. Wilson,

Deputy Director, National Institute of Environmental Health Sciences.

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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