APPENDIX I

FEDERAL REGISTER NOTICES AND PUBLIC COMMENTS

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APPENDIX I1

FEDERAL REGISTER NOTICES

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Toxicology Program (NTP); National Institute of Environmental Health Sciences (NIEHS); National Institutes of Health (NIH); NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Request for Public Comment on the Nomination for Ocular Toxicity Test Methods and Related Activities and Request for Data on Chemicals Evaluated by *In Vitro* or *In Vivo* Ocular Irritancy Test Methods

SUMMARY: On behalf of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), NICEATM requests (1) public comment on four test methods for ocular toxicity and related activities nominated to the ICCVAM by the U.S. Environmental Protection Agency (EPA), (2) public comment on ICCVAM's recommended actions for the nomination, and (3) data from completed studies on chemicals and products tested for ocular irritancy using *in vitro* and/or *in vivo* test methods. This data will be used to (1) evaluate the validation status of existing *in vitro* test methods for ocular irritancy/corrosion and (2) develop a list of substances with high quality *in vivo* data that can be considered as reference chemicals for future validation studies.

NICEATM welcomes data generated using standardized *in vitro* test methods used to identify severe, moderate, mild, or non-irritating substances. Test methods for identifying severe (irreversible) ocular irritation/corrosion for which data are sought include, but are not limited to the four methods nominated by the EPA: (1) The Bovine Corneal Opacity and Permeability (BCOP) test, (2) the Isolated Rabbit Eye (IRE) test or the Rabbit Enucleated Eye Test (REET), (3) the Isolated Chicken Eye (ICE) test or the Chicken Enucleated Eye Test (CEET), and (4) the Hen's Egg Test—Chorion Allantoic Membrane (HET–CAM). In addition, high quality data from standardized ocular irritancy test methods using rabbits (*e.g.*, EPA 1998; UN 2003) and *in vivo* data generated from procedures/protocols that might alleviate or reduce pain and suffering (*e.g.*, topical and systemic analgesics) in test animals are requested.

Background Information

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) unanimously recommended at its meeting in August 2003 that NICEATM focus efforts on test methods for ocular irritancy and possibly hold a workshop and/or develop a background document on available methods. In October 2003, the EPA nominated the following activities to ICCVAM: (1) Evaluate the validation status of four *in vitro* ocular toxicity test methods: the BCOP, IRE or the REET, ICE or CEET, and HET–CAM, (2) identify and develop *in vivo* ocular toxicity reference data to support the validation of *in vitro* test methods, (3) explore ways of alleviating pain and suffering from current *in vivo* ocular toxicity testing, and (4) review the state of the science and the availability of *in vitro* test methods for assessing mild or moderate ocular irritants. ICCVAM endorsed the review of the methods as a high priority and recommended that NICEATM develop Background Review Documents for BCOP, IRE, ICE, and HET–CAM. ICCVAM also recommended that NICEATM convene an expert panel to independently review the validation status of these four methods and propose standardized protocols for these test methods.

As part of the nomination review process, the NICEATM invites public comments on the EPA nomination to ICCVAM and the ICCVAM's recommended actions. In addition, ICCVAM and NICEATM are collaborating with the European Center for the Validation of Alternative Methods (ECVAM) to evaluate the validation status of *in vitro* methods for assessing ocular irritation/corrosion. In response to the SACATM recommendation, the EPA nomination and ICCVAM's recommended actions, and the NICEATM/ICCVAM collaboration with ECVAM, NICEATM also requests the submission of data from completed studies on chemicals and products tested for ocular irritancy using *in vitro* and/or *in vivo* test methods. This data will be used to evaluate the validation status of existing *in vitro* test methods for ocular irritancy/corrosion and to develop a list of substances with high quality *in vivo* data that can be considered as reference chemicals for future validation studies. Information on the expert panel evaluation(s) will be announced in a future **Federal Register** notice.

Public Comment and Submission of Chemical and Protocol Information and Test Data

Public comment and data and other information submitted in response to this notice should be sent to NICEATM (Dr. William S. Stokes, Director, NICEATM, NIEHS, 79 T.W. Alexander Drive, P.O. Box 12233, MD EC–17, Research Triangle Park, NC 27709, (phone) 919–541–2384, (fax) 919–541–0947, *iccvam@niehs.nih.gov*) and received by May 24, 2004. Data and other information received by this date will be forwarded to the ICCVAM and the ICCVAM Ocular Toxicity Working Group (OTWG) for their consideration. Data and other information received after this date will be periodically compiled and added to the database maintained by NICEATM. All information submitted in response to this notice will be made publicly available upon request to NICEATM.

When submitting data or information on protocols, please reference this **Federal Register** notice and provide appropriate contact information (name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization, as applicable). NICEATM prefers data to be submitted as copies of pages from applicable study notebooks and/or study reports, if available. Each submission for a chemical should preferably include the following information, as appropriate:

- Common and trade name;
- Chemical Abstracts Service Registry Number (CASRN);
- Chemical and/or product class;
- Commercial source;
- *In vitro* test protocol used;
- Rabbit eye test protocol used;
- Human eye test protocol used;
- Individual animal/human or *in vitro* responses at each observation time (*i.e.*, raw data);
- The extent to which the study complies with national/international Good Laboratory Practice (GLP) guidelines;
- Date and testing organization.

Those persons submitting data on chemicals tested for ocular irritancy in rabbits are referred to the ICCVAM/NICEATM Web site (*http://iccvam.niehs.nih.gov/methods/eyeirrit.htm*) for an example of the type of experimental animal study information and data requested in this notice.

In Vitro Ocular Irritancy Chemical Tests: BCOP, HET–CAM, ICE, and IRE

NICEATM welcomes public comment on and the submission of data from the four *in vitro* test methods used to identify severe (irreversible) ocular irritation/corrosion nominated by the EPA: BCOP, HET–CAM, ICE, and IRE. This information will be used to evaluate the validation status of these test method protocols and to identify any additional development and/or validation that might be helpful in advancing the usefulness of the proposed test methods. ICCVAM anticipates recommending a standardized protocol for each of the four test methods. ICCVAM also will use existing data and protocols as the basis for development of proposed performance standards that structurally and functionally similar test methods should meet or exceed. Because test methods for identifying severe eye irritants/corrosives are of high priority, NICEATM especially requests data on chemicals identified by these four methods as severe irritants, although data on mildly irritating and non-irritating substances also are welcome.

Other *In Vitro* Ocular Irritancy Methods

NICEATM also requests the submission of data and information for standardized *in vitro* ocular irritancy methods, other than the four identified above, and methods that might accurately identify non-irritating and mild to moderate irritants. Detailed test method protocols and other related information for these potential test methods should be submitted along with the data.

In Vivo Test Methods for Ocular Irritancy

NICEATM requests the submission of high quality *in vivo* data that might be used to identify appropriate reference chemicals for future validation studies of *in vitro* ocular irritancy test methods. This data would be used to construct a database of *in vivo* data to assess interlaboratory variability, as well as to support validation efforts. Data are sought from studies conducted to comply with Federal or other national/international testing requirements, but may not be publicly available because: (1) The data were submitted to regulatory authorities, but are proprietary and cannot be released to the public by regulatory authorities or (2) there is no requirement to submit the data to regulatory authorities. In addition to data from studies in animals, NICEATM also welcomes the submission of data from human studies, including any human post-marketing or occupational exposure/surveillance data that might be available.

Procedures for Reducing or Eliminating Pain and Suffering during *In Vivo* Ocular Irritancy Testing

NICEATM requests the submission of information and data from *in vivo* methods, procedures, and/or strategies that may reduce or eliminate the pain and suffering associated with current *in vivo* eye irritation methods, such as those using topical or systemic analgesics.

Background Information on ICCVAM and NICEATM

ICCVAM is an interagency committee composed of representatives from 15 Federal regulatory and research agencies that use or generate toxicological information. ICCVAM promotes the development, validation, evaluation, and regulatory acceptance of toxicological test methods that improve agencies' ability to make decisions on health risks, while refining, reducing and replacing animal use wherever possible.

The ICCVAM Authorization Act of 2000 (Pub. L. 106–545, available at *http://iccvam.niehs.nih.gov/about/PL106545.htm*) establishes ICCVAM as a permanent interagency committee of the NIEHS under the NICEATM. NICEATM provides scientific support for ICCVAM and 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 following Web site: *http://iccvam.niehs.nih.gov.*

References

EPA 1998. Health Effects Test Guidelines, OPPTS 870.2500, Acute Eye Irritation, EPA 712–C–98–195. Available: *http://www.epa.gov.opptsfrs/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Drafts/870-2400.pdf.*

UN. 2003. Globally Harmonized System of Classification and Labelling of Chemicals (GHS). (ST/SG/AC.10/30). United Nations, New York and Geneva. Available: *http://www.unece.org/trans/danger/publi/ghs/officialtext.html.*

Dated: March 15, 2004.

Kenneth Olden,

Director, National Institute of Environmental Health Sciences.

[FR Doc. 04–6487 Filed 3–23–04; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH), National Toxicology Program (NTP); Request for Nominations of Scientific Experts for Independent Expert Panel Evaluations and/or other Reviews of In Vitro Testing Methods for Identifying Potential Ocular Irritants

Summary

The 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) is seeking nominations of scientific experts to evaluate the validation status of in vitro test methods for determining the potential ocular irritancy of chemicals and other substances. The experts will serve on future independent expert panel(s) or participate at other similar meetings and provide input on the usefulness, limitations, accuracy, and reliability of test methods proposed for identifying whether and to what extent substances may cause reversible or irreversible eye damage. The initial review activity will evaluate test methods that may be used to identify severe irreversible ocular irritation/corrosion. Applicable test methods anticipated for review include, but are not limited to: (1) The Bovine Corneal Opacity and Permeability (BCOP) test; (2) the Hen's Egg Test—Chorion Allantoic Membrane (HET-CAM); (3) the Isolated Rabbit Eye (IRE) test; and (4) the Isolated Chicken Eye (ICE) test. Details about future meetings to evaluate the validation status of in vitro ocular toxicity test methods, including the date, location and availability of background documents, will be announced in the **Federal Register** and posted on the ICCVAM/NICEATM website *(http://iccvam.niehs.nih.gov)*.

Request for Nominations of Experts

NICEATM invites nominations of scientists with relevant knowledge and experience that can serve on independent expert panels or participate at other similar meetings to evaluate in vitro ocular toxicity test methods. Areas of relevant expertise include, but are not limited to: human and animal ophthalmology, with an emphasis on evaluation and treatment of chemical injuries; in vivo ocular toxicity testing; in vitro ocular toxicology (particularly experience with BCOP, IRE, ICE, and/or HET–CAM); test method validation; and biostatistics. Each nomination should include the person's name, affiliation, contact information (*i.e.*, mailing address, e-mail address, telephone and fax numbers), a brief summary of relevant experience and qualifications, and curriculum vitae, if possible. Nominations should be sent to NICEATM by mail, fax, or e-mail within 45 days of the publication date of this notice. Correspondence should be directed to Dr. William Stokes, Director, NICEATM, NIEHS, 79 T.W. Alexander Dr., MD EC–17, P.O. Box 12233, Research Triangle Park, NC 27709; telephone: 919–541–2384; fax: 919–541–0947; e-mail: *iccvam@niehs.nih.gov.*

SUPPLEMENTARY INFORMATION: In August 2003, the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) recommended that ICCVAM evaluate certain in vitro test methods for ocular toxicity that could be used to identify substances that cause irreversible ocular damage. The SACATM recommended that NICEATM and ICCVAM prepare a background review document and convene a workshop or other appropriate review activity. In October 2003, EPA submitted a nomination to ICCVAM that included a request to: (1) Review the validation status of four in vitro ocular test methods with the potential to screen chemicals for severe eye irritation or corrosion (BCOP, IRE, ICE, HET–CAM); (2) review the state of the science for other in vitro methods for assessing moderate or mild eye irritation; (3) obtain good quality in vivo eye irritation/corrosion reference data; and (4) to review ways to alleviate pain and suffering which might arise from current in vivo eye irritation testing. ICCVAM endorsed this nomination as a high priority. NICEATM published a **Federal Register** notice on March 24, 2004 (Vol. 69, No. 57, pages 13959–13861) inviting public comment on the nomination and related activities.

NICEATM is preparing Background Review Documents on in vitro ocular test methods that will contain comprehensive summaries of available data, an analysis of the accuracy and reliability of available test method protocols, and related information characterizing the current validation status of these assays. NICEATM requested data on ocular irritancy for chemicals tested using in vivo and in vitro test methods in the March 24 **Federal Register** notice. Applicable data received in response to this notice will be included in the Background Review Documents and used to assess the performance of in vitro ocular toxicity test methods. Conclusions and recommendations from independent evaluations will be made publicly available and considered by ICCVAM in developing its recommendations on in vitro ocular toxicity test methods. ICCVAM recommendations will address the usefulness and limitations of the test methods for regulatory testing purposes and may include recommended standardized protocols, performance standards, and reference chemicals for future validation studies.

Background Information on ICCVAM and NICEATM

ICCVAM is an interagency committee composed of representatives from fifteen Federal regulatory and research agencies that use or generate toxicological information. ICCVAM promotes the development, validation, regulatory acceptance, and national and international harmonization of toxicological test methods that more accurately assess the safety or hazards of chemicals and products; and test methods that refine, reduce and replace animal use. The ICCVAM Authorization Act of 2000 (Pub. L. 106–545, available at *http://iccvam.niehs.nih.gov/about/PL106545.htm*) established ICCVAM as a permanent interagency committee of the NIEHS under the NICEATM. NICEATM administers the ICCVAM and provides scientific support for ICCVAM and 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 following Web site: *http://iccvam.niehs.nih.gov.*

Dated: April 9, 2004.

Samuel H. Wilson,

Deputy Director, National Institute of Environmental Health Sciences.

[FR Doc. 04–9032 Filed 4–20–04; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Toxicology Program; National Institute of Environmental Health Sciences (NIEHS); National Institutes of Health (NIH) Notice of an Expert Panel Meeting To Assess the Current Validation Status of In Vitro Testing Methods for Identifying Potential Ocular Irritants; Request for Comments

Summary

Notice is hereby given of a meeting sponsored by the NIEHS and the National Toxicology Program (NTP), and organized by the 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). At this meeting, an expert panel ("Panel") will assess the current validation status and develop recommendations for further validation of in vitro test methods proposed for identifying substances that may cause serious eye damage. The meeting will take place on January 11–12, 2005, from 8:30 a.m. to 5 p.m., at the National Institutes of Health (NIH), Natcher Center, Bethesda, MD. The meeting is open to the public with attendance limited only by the space available.

Evaluation of In Vitro Ocular Test Methods Background

In August 2003, the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) recommended that ICCVAM review the validation status of screening test methods that could be used to identify severe and irreversible ocular effects and carry out appropriate reviews of these test methods. In October 2003, the U.S. Environmental Protection Agency nominated several ocular-related activities to ICCVAM including evaluation of the validation status of four in vitro ocular toxicity test methods for screening for severe/irreversible ocular effects: (1) The Bovine Corneal Opacity and Permeability (BCOP) test; (2) the Hen's Egg Test—Chorion Allantoic Membrane (HET–CAM); (3) the Isolated Rabbit Eye (IRE) test; and (4) the Isolated Chicken Eye (ICE) test. ICCVAM endorsed the review of the methods as a high priority and recommended that Background Review Documents be developed for each method by NICEATM in collaboration with the ICCVAM Ocular Toxicity Working Group. ICCVAM also

recommended that an expert panel be convened to independently review the validation status of these methods and the proposed, standardized, test method protocols.

A request for public comment on the nomination of these and other ocular toxicity test methods and related activities and a request for data on chemicals evaluated by in vitro or in vivo ocular irritancy test methods was previously published in the **Federal Register** (Vol. 69, No. 57, pp. 13859–13861, March 24, 2004, available at *http://iccvam.niehs.nih.gov/*). Additionally, NICEATM solicited the nomination of scientific experts for independent expert panel evaluations and/or reviews of in vitro testing methods for identifying potential ocular irritants through the **Federal Register** (Vol. 69, No. 77, pg. 21565, April 21, 2004, available at *http://iccvam.niehs.nih.gov/*). This notice also announced that ICCVAM and NICEATM would coordinate an expert panel meeting to evaluate in vitro ocular test methods for their ability to detect severe and irreversible ocular irritants. No additional methods for identifying severe/irreversible ocular effects other than the four named above were identified in response to the **Federal Register** notices.

NICEATM has prepared Background Review Documents (BRDs) on the four test methods nominated by the EPA (BCOP, HET-CAM, IRE and ICE). Each of the BRDs contains comprehensive summaries of available data, analyses of the accuracy and reliability of the available test method protocols, and related information characterizing the current validation status of these assays. At this meeting, the Panel will review each of the four BRDs and develop conclusions and recommendations on the following:

- The current usefulness and limitations of the test methods for identifying severe/irreversible ocular irritants and corrosives.
- The adequacy of the specific protocols recommended for future validation and testing studies.
- The adequacy of recommended test method validation studies.
- The adequacy and appropriateness of substances recommended for future validation studies.

Agenda

The public meeting will take place January 11–12, 2005, at the NIH Campus, Natcher Center, Bethesda, MD (a map of the NIH Campus and other visitor information are available at *http://www.nih.gov/about/visitor/index.htm*). The meeting will begin at 8:30 a.m. each day and conclude at approximately 5 p.m. A preliminary agenda is given below. A detailed agenda and roster of the expert panel members will be available two weeks prior to the meeting on the ICCVAM/NICETATM Web site (*http://iccvam.niehs.nih.gov*) or by contacting NICEATM (contact information below). Persons needing special assistance, such as sign language interpretation or other special accommodations, should contact NICEATM at least seven business days in advance of the meeting.

On the morning of January 11th, there will be a brief orientation on ICCVAM and the ICCVAM test method review process, followed by the Panel's evaluation of the BRDs for the ICE and BCOP assays. It is anticipated that review of the HET–CAM assay will continue on the morning of January 12th after which the review of the BRD for the IRE assay will take place. The Panel will evaluate the current status of each of the four different types of in vitro assays and develop recommendations regarding their future validation and use.

Availability of Background Review Documents

NICEATM has prepared four BRDs, one for each of the assays being evaluated. Copies of each BRD can be obtained on the ICCVAM/NICEATM Web site at *http://iccvam.niehs.nih.gov*, or by contacting NICEATM, NIEHS, PO Box 12233, MD EC–17, Research Triangle Park, NC, 27709, (phone) 919–541–3398, (fax) 919–541–0947, (email) *iccvam@niehs.nih.gov*.

Request for Comments

NICEATM invites the submission of written comments on each of the BRDs. When submitting written comments please include appropriate contact information (name, affiliation, mailing address, phone, fax, email and sponsoring organization, if applicable). Written comments and additional information should be sent by mail, fax, or email to Dr. William Stokes, Director of NICEATM, at the address listed above not later than December 30, 2004. Written comments will be placed on the ICCVAM/NICEATM website and made available to the Panel, ICCVAM agency representatives and experts, and attendees at the meeting.

The meeting is open to the public and time will be provided for the presentation of public oral comments at designated times during the peer review. Members of the public who wish to present oral statements at the meeting (one speaker per organization) should contact NICEATM (at the address above) no later than noon on January 5, 2005. Speakers will be assigned on a consecutive basis and up to seven minutes will be allotted per speaker. Persons registering to make comments are asked to provide a written copy of their statement by January 5th, so that copies can be distributed to the Panel prior to the meeting or if this is not possible to bring 40 copies to the meeting. Written statements can supplement and expand the oral presentation. Each speaker is asked to provide contact information (name, affiliation, mailing address, phone, fax, email and sponsoring organization, if applicable) when registering to make oral comments.

Summary minutes and a final report of the Panel will be available following the meeting at the ICCVAM/NICEATM Web site (*http://iccvam.niehs.nih.gov*).

Background Information on ICCVAM and NICEATM

ICCVAM is an interagency committee charged with the technical review and evaluation of new, revised, and alternative test methods applicable for specific regulatory uses. The committee is composed of representatives from 15 Federal regulatory and research agencies that use or generate toxicological information. ICCVAM promotes the development, validation, regulatory acceptance, and national and international harmonization of toxicological test methods that more accurately assess the safety or hazards of chemicals and products and that refine, reduce, or replace animal use. The ICCVAM Authorization Act of 2000 (Pub. L. 106–545, available at http://iccvam.niehs.nih.gov/about/PL106545.htm) established ICCVAM as a permanent interagency committee of the NIEHS under the NICEATM. NICEATM administers the ICCVAM and provides scientific support for ICCVAM and 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 following Web site: *http://iccvam.niehs.nih.gov*.

Dated: October 21, 2004.

Samuel Wilson,

Deputy Director, National Institute of Environmental Health Sciences.

[FR Doc. 04–24481 Filed 11–2–04; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

National Toxicology Program; National Institute of Environmental Health Sciences (NIEHS); National Institutes of Health (NIH) Notice of Additional Data and Analyses for the Assessment of the Current Validation Status of In Vitro Testing Methods for Identifying Potential Ocular Irritants

Summary

The National Toxicology Program (NTP) Interagency Center for the

Evaluation of Toxicological Methods (NICEATM) recently published a notice in the **Federal Register** (Vol. 69, No. 212, pages 64081–2, November 3, 2004) announcing the availability of and requesting comments on Background Review Documents (BRDs) for four *in vitro* assays proposed for identifying potential ocular corrosives and severe irritants. Notice is hereby given of the availability of additional data and analyses for the Hen's Egg Test-Chorion Allantoic Membrane (HET–CAM) assay. Copies of the additional analyses and any other updates on information relevant to this meeting can be obtained on the ICCVAM/NICEATM Web site at *http://iccvam.niehs.nih.gov* or by contacting NICEATM [NIEHS, P.O. Box 12233, MD EC–17, Research Triangle Park, NC, 27709, (phone) (919) 541–3398, (fax) (919) 541–0947, (e-mail) *iccvam@niehs.nih.gov*].

Interested parties are invited to check the ICCVAM/NICEATM Web site periodically for additional information and/or analyses for this meeting.

Dated: November 23, 2004.

Samuel H. Wilson,

Deputy Director, National Institute of Environmental Health Sciences.

[FR Doc. 04–26594 Filed 12–2–04; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Toxicology Program (NTP); National Institute of Environmental Health Sciences (NIEHS); National Institutes of Health (NIH); NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Second Request for Data on Chemicals Evaluated by In Vitro or In Vivo Ocular Irritancy Test Methods

Summary

The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and NICEATM are collaborating with the European Center for the Validation of Alternative Methods (ECVAM) to evaluate the validation status of in vitro methods for assessing ocular irritation/corrosion. Data was previously requested (**Federal Register**, Vol. 69, No. 57, pp. 13859–13861, March 24, 2004, available at *http://iccvam.niehs.nih.gov/*) and used to prepare draft Background Review Documents (BRD) for four methods [(1) The Bovine Corneal Opacity and Permeability (BCOP) test; (2) the Isolated Rabbit Eye (IRE) test or the Rabbit Enucleated Eye Test (REET); (3) the Isolated Chicken Eye (ICE) test or the Chicken Enucleated Eye Test (CEET); and (4) the Hen's Egg Test—Chorion Allantoic Membrane (HET–CAM)], and to compile a database of *in vivo* data. ICCVAM and NICEATM are now finalizing these BRDs and want to ensure the inclusion of all available data. NICEATM is therefore issuing this second request for data generated using standardized *in vitro* and *in vivo* test methods used to identify severe, moderate, mild, or non-irritating substances. Test methods for identifying severe (irreversible) ocular irritation/corrosion for which data are sought include, but are not limited to: (1) The BCOP test; (2) the IRE test; (3) the ICE test; and (4) the HET–CAM. In addition, high quality data from standardized ocular irritancy test methods using rabbits (*e.g.*, EPA 1998; UN 2003) and *in vivo* data generated from procedures/protocols that might alleviate or reduce pain and suffering (*e.g.*, topical and systemic analgesic) in test animals are requested. These data will be used to evaluate the validation status of existing in vitro test methods for ocular irritancy/corrosion and to develop a list of substances with high quality *in vivo* data that can be considered as reference chemicals for future validation studies. Data from other *in vitro* methods used to assess reversible ocular irritation effects or non-irritation are also requested.

Submission of Chemical and Protocol Information and Test Data

Data and other information submitted in response to this notice should be sent to NICEATM [Dr. William S. Stokes, Director, NICEATM, NIEHS, 79 T. W. Alexander Drive, P.O. Box 12233, MD EC–17, Research Triangle Park, NC 27709, (phone) 919–541–2384, (fax) 919–541–0947, *iccvam@niehs.nih.gov*] and received by March 30, 2005. Data and other information received by this date will be compiled and added to the database maintained by NICEATM and utilized where appropriate for the final BRDs on the four methods listed above. Data received after this date will also be considered and used where applicable for future evaluation activities. All information submitted in response to this notice will be made publicly available upon request to NICEATM.

When submitting data or information on protocols, please reference this **Federal Register** notice and provide appropriate contact information (name, affiliation, mailing address, phone, fax, e-mail, and sponsoring organization, as applicable). NICEATM prefers data to be submitted as copies of pages from study notebooks and/or study reports, if available. Each submission for a chemical should preferably include the following information, as appropriate:

- Common and trade name
- Chemical Abstracts Service Registry Number (CASRN)
- Chemical and/or product class
- Commercial source
- *In vitro* test protocol used
- Rabbit eye test protocol used
- Human eye test protocol used
- Individual animal/human or *in vitro* responses at each observation time (*i.e.*, raw data).
- The extent to which the study complies with national/international Good Laboratory Practice (GLP) guidelines
- Date and testing organization

Those persons submitting data on chemicals tested for ocular irritancy in rabbits are referred to the ICCVAM/NICEATM Web site (*http://iccvam.niehs.nih.gov/methods/eyeirrit.htm*) for an example of the type of experimental animal study information and data requested in this notice.

In Vitro Ocular Irritancy Chemical Tests: BCOP, HET–CAM, ICE, and IRE

NICEATM is especially interested in data from four *in vitro* test methods used to identify severe (irreversible) ocular irritation/corrosion: BCOP, HET–CAM, ICE, and IRE. Because test methods for identifying severe eye irritants/corrosives are of high priority, NICEATM especially requests data on chemicals identified by these four methods as severe irritants, although data on mildly irritating and non-irritating substances are also welcome.

Other *In Vitro* Ocular Irritancy Methods

NICEATM also requests the submission of data and information for standardized *in vitro* ocular irritancy methods, other than the four identified above, and methods that might be used to identify non-irritating and mild to moderate irritants. Detailed test method protocols and other related information for these potential test methods should be submitted along with the data.

In Vivo Test Methods for Ocular Irritancy

NICEATM requests the submission of high quality *in vivo* data that might be used to identify appropriate reference chemicals for future validation studies of *in vitro* ocular irritancy test methods. Data are sought from studies conducted to comply with federal or other national/international testing requirements, but may not be publicly available because: (1) The data were submitted to regulatory authorities, but are proprietary and cannot be released to the public by regulatory authorities, or (2) there is no requirement to submit the data to regulatory authorities. In addition to data from studies in animals, NICEATM also welcomes the submission of data from human studies including any human post-marketing or occupational exposure/surveillance data that might be available.

Procedures for Reducing or Eliminating Pain and Suffering during *In Vivo* Ocular Irritancy Testing

NICEATM requests the submission of information and data from *in vivo* methods, procedures, and/or strategies that may reduce or eliminate the pain and suffering associated with current *in vivo* eye irritation methods, such as those using topical or systemic analgesics.

Background Information

In August 2003, the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) unanimously recommended that NICEATM focus efforts on test methods for ocular irritancy and possibly hold a workshop and/or develop a background document on available methods. In October 2003, the U.S. Environmental Protection Agency nominated the following activities to ICCVAM: (1) Evaluate the validation status of the four *in vitro* ocular toxicity test methods (BCOP, IRE, ICE, and HET–CAM), (2) identify and develop *in vivo* ocular toxicity reference data to support the validation of *in vitro* test methods, (3) explore ways of alleviating pain and suffering from current *in vivo* ocular toxicity testing, and (4) review the state of the science and the availability of *in vitro* test methods for assessing mild or moderate ocular irritants. ICCVAM endorsed the review of these methods as a high priority and recommended that NICEATM develop Background Review Documents for BCOP, IRE, ICE, and HET–CAM. NICEATM convened an independent expert panel on January 11–12, 2005, to review the validation status of these four methods and develop conclusions and recommendations on standardized protocols and reference chemicals for future testing and validation studies. Availability of the expert panel's report will be announced in a future **Federal Register** notice.

Background Information on ICCVAM and NICEATM

ICCVAM is an interagency committee composed of representatives from fifteen 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, and replace animal use. The ICCVAM Authorization Act of 2000 (P.L. 106–545, available at *http://iccvam.niehs.nih.gov/about/PL106545.htm*) establishes ICCVAM as a permanent interagency committee of the NIEHS under the NICEATM. NICEATM administers and provides scientific support for the ICCVAM. 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 following Web site: *http://www.iccvam.niehs.nih.gov*.

References

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UN 2003. Globally Harmonized System of Classification and Labelling of Chemicals (GHS). [ST/SG/AC.10/30]. United Nations, New York and Geneva. Available: *http://www.unece.org/trans/danger/publi/ghs/officialtext.html*.

Dated: February 17, 2005.

Samuel H. Wilson,

Deputy Director, National Institute of Environmental Health Sciences.

[FR Doc. 05–3831 Filed 2–25–05; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Toxicology Program; National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Availability of Expert Panel Report on the Evaluation of the Current Validation Status of *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants

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

ACTION: Availability of report and request for comments.

SUMMARY: The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) announces the availability of a report entitled, "The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Expert Panel Evaluation of the Current Validation Status of *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants." The NICEATM invites public comment on the expert panel report. Copies of the expert 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 and additional information should be received by noon on May 5, 2005.

ADDRESSES: Comments and additional information should be sent by mail, fax, or e-mail to Dr. William S. Stokes, Director of NICEATM, at 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, 79 T.W. Alexander Drive, Building 4401, Room 3128, Research Triangle Park, NC 27709.

FOR FURTHER INFORMATION CONTACT: Dr. William S. Stokes, Director of NICEATM, (phone) 919–541–2384, (e-mail) *niceatm@niehs.nih.gov*.

SUPPLEMENTARY INFORMATION:

Background

On January 11 and 12, 2005, NICEATM and ICCVAM held an expert panel meeting to evaluate the validation status for four *in vitro* ocular test methods nominated by the EPA: (1) The Bovine Corneal Opacity and Permeability (BCOP) test; (2) the Hen's Egg Test—Chorion Allantoic Membrane (HET–CAM); (3) the Isolated Rabbit Eye (IRE) test; and (4) the Isolated Chicken Eye (ICE) test. At this meeting, the expert panel reviewed the Background Review Document (BRD) for each method and was asked to:

- Evaluate the extent and adequacy that each method's BRD addresses the applicable ICCVAM validation and acceptance criteria based on available information and data, or will address the criteria in proposed studies, focused on identifying ocular corrosives and severe irritants in a tiered testing strategy.
- Develop conclusions and recommendations on:

—The current usefulness and limitations of each of the four test methods for identifying ocular corrosives and severe/irreversible irritants.

—The test method protocol that should be used for future testing and validation studies.

—The adequacy of proposed optimization and/or validation studies.

—The adequacy of reference substances proposed for future validation studies.

The expert panel's conclusions and recommendations on the four test methods are described in "The ICCVAM Expert Panel Evaluation of the Current Validation Status of *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants".

Prior to the expert panel meeting, NICEATM issued several **Federal Register** notices to (1) request public comment on the EPA nomination of ocular toxicity test methods and related activities and request data on chemicals evaluated by *in vitro* or *in vivo* ocular irritancy test methods (**Federal Register**, Vol. 69, No. 57, pp. 13859–13861, March 24, 2004, available at *http://iccvam.niehs.nih.gov/*); (2) request the nomination of scientific experts to serve on the expert panel (**Federal Register**, Vol. 69, No. 77, pg. 21565, April 21, 2004, available at *http://iccvam.niehs.nih.gov/*); and (3) request public comments on the BRDs prepared by NICEATM for each of the four test methods (**Federal Register**, Vol. 69, No. 212, pp. 64081–64082, November 3, 2004, and public comments are available at *http://iccvam.niehs.nih.gov/*).

Request for Comments

NICEATM invites the submission of written comments on the expert panel report. When submitting written comments please include appropriate contact information (name, affiliation, mailing address, phone, fax, email and sponsoring organization, if applicable). All written comments received by the deadline listed above will be posted on the ICCVAM/NICEATM Web site and made available to ICCVAM.

ICCVAM will consider the expert panel report and any written public comments received on that report as it prepares final ICCVAM test method recommendations for the four *in vitro* ocular test methods. An ICCVAM test method evaluation report, which includes the ICCVAM recommendations, will be forwarded to appropriate Federal agencies for their consideration. This report also will be available to the public on the ICCVAM/NICEATM Web site and by request to NICEATM.

Background Information on ICCVAM and NICEATM

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, and replace animal use. The ICCVAM Authorization Act of 2000 (Pub. L. 106–545, available at *http://iccvam.niehs.nih.gov/about/PL106545.htm*) establishes ICCVAM as a permanent interagency committee of the NIEHS under the NICEATM. NICEATM administers the 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 following Web site: *http://iccvam.niehs.nih.gov.*

Dated: March 9, 2005.

Samuel Wilson,

Deputy Director, National Institute of Environmental Health Sciences.

[FR Doc. 05–5473 Filed 3–18–05; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Toxicology Program (NTP); NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Ocular Toxicity Scientific Symposia: Mechanisms of Chemically-Induced Ocular Injury and Recovery and Minimizing Pain and Distress in Ocular Toxicity Testing

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

ACTION: Meeting announcement.

SUMMARY: The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the NICEATM announce two upcoming scientific symposia entitled, "Mechanisms of Chemically-Induced Ocular Injury and Recovery" and "Minimizing Pain and Distress in Ocular Toxicity Testing."

DATES: The first symposium, "Mechanisms of Chemically-Induced Ocular Injury and Recovery," will be held on May 11 and 12, 2005. The second symposium, "Minimizing Pain and Distress in Ocular Toxicity Testing," will be held on May 13, 2005. In order to facilitate planning for this meeting, persons wishing to attend the symposia are asked to register via the ICCVAM/NICEATM Web site (*http://iccvam.niehs.nih.gov*) by May 2, 2005.

ADDRESSES: Both symposia will be held at the National Institutes of Health, Natcher Conference Center, 45 Center Drive, Bethesda, MD, 20892. An updated agenda and other information will be available on the NICEATM/ICCVAM Web site (*http://iccvam.niehs.nih.gov*) and can also be obtained from NICEATM (*see* **FOR FURTHER INFORMATION CONTACT** below).

FOR FURTHER INFORMATION CONTACT: All correspondence should be submitted to the Director of NICEATM (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*. Courier address: NICEATM, 79 T.W. Alexander Drive, Building 4401, Room 3128, Research Triangle Park, NC 27709.

SUPPLEMENTARY INFORMATION:

Background

The symposium, "Mechanisms of Chemically-Induced Ocular Injury and Recovery," will review the state-of-the-science and understanding of the pathophysiology and mechanisms of chemically-induced ocular injury and recovery (reversibility vs. irreversibility). The symposium will seek to identify research needed to address current knowledge gaps and that will advance the development and validation of test systems for regulatory testing that provide for protection of human health while reducing, refining (less pain and distress), and/or replacing the use of animals.

The symposium, "Minimizing Pain and Distress in Ocular Toxicity Testing," will review current understanding of the sources and mechanisms of pain and distress in ocular toxicity testing; identify current best practices for preventing, recognizing, and alleviating ocular pain and distress; and identify additional research, development, and validation studies necessary to support scientifically valid ocular testing procedures that avoid pain and distress.

Preliminary Agenda

Mechanisms of Chemically-Induced Ocular Injury and Recovery, May 11 and 12, 2005, National Institutes of Health, Natcher Conference Center, Room E1/E2, 45 Center Drive, Bethesda, MD 20892 (A photo ID is required to access the NIH campus).

Day 1 Wednesday, May 11, 2005

8:30 a.m.

- Welcome and Introduction of Symposium Objectives
- Session 1—Overview of Recent Initiatives
- Session 2—Current Ocular Injury and Toxicity Assessments
- Session 3—Mechanisms and Biomarkers of Ocular Injury and Recovery
- Discussion

5 p.m.

Adjourn Day 1

Day 2 Thursday, May 12, 2005

8:30 a.m.

- Session 4—In Vitro Models of Ocular Injury and Recovery
- Discussion
- Session 5—In Vivo Quantitative Objective Endpoints to Support Development and Validation of Predictive In Vitro Models
- Discussion
- Summary of Symposium Discussions

5 p.m.

Adjourn Meeting

Minimizing Pain and Distress in Ocular Toxicity Testing, May 13, 2005, National Institutes of Health, Natcher Conference Center, Balcony B, 45 Center Drive, Bethesda, MD 20892 (A photo ID is required to access the NIH campus).

8:30 a.m.

- Welcome and Introduction of Symposium Objectives
- Session 1—Recognition and Sources of Pain in Ocular Injuries and Safety Testing
- Discussion: Clinical Signs, Lesions and Other Biomarkers of Pain and Distress in Animals
- Session 2—Alleviation and Avoidance of Ocular Injury and Pain
- Discussion
- Session 3—Biomarkers that Can Serve as Earlier Humane Endpoints for Ocular Studies
- Discussion
- Closing Remarks

5 p.m.

Adjourn Meeting

Attendance and Registration

The symposia will be held on May 11–13, 2005, from 8:30 a.m. until adjournment and are open to the public with attendance limited only by the space available. Individuals who plan to attend are strongly encouraged to register with NICEATM via the NICEATM/ICCVAM Web site (*http://iccvam.niehs.nih.gov*) by May 2, 2005. A map of the NIH campus, including visitor parking, is available at *http://www.nih.gov/about/visitor/index.htm#directions*. Please note that a photo ID is required to access the NIH campus. Persons needing special assistance, such as sign language interpretation or other reasonable accommodation in order to attend, are asked to notify NICEATM at least 7 business days in advance of the meeting (*see* **FOR FURTHER INFORMATION CONTACT** above).

Availability of Meeting Materials

An updated agenda and other additional information will be available on the ICCVAM Web site and upon request from NICEATM (*see* **FOR FURTHER INFORMATION CONTACT** above). Those persons who register by the deadline will be provided with materials for the meeting upon on-site check-in at the meeting.

Background Information on ICCVAM and NICEATM

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 while refining (less pain and distress), reducing, and replacing animal use. The ICCVAM Authorization Act of 2000 (Pub. L. 106–545, available at *http://iccvam.niehs.nih.gov/about/PL106545.htm)* establishes ICCVAM as a permanent interagency committee of the NIEHS under the NICEATM. NICEATM administers the ICCVAM and provides scientific and operational support for ICCVAM-related activities. NICEATM and ICCVAM work collaboratively to evaluate new, improved, and alternative test methods applicable to the needs of Federal agencies. Additional information about ICCVAM and NICEATM can be found at the following Web site: *http://iccvam.niehs.nih.gov.*

Dated: March 31, 2005.

Kenneth Olden,

Director, National Toxicology Program.

[FR Doc. 05–7002 Filed 4–7–05; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Toxicology Program (NTP); NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Availability of Revised Analyses and Proposed Reference Substances for In Vitro Test Methods for Identifying Ocular Corrosives and Severe Irritants

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

ACTION: Availability of analyses and proposed reference substances and request for comments.

SUMMARY: NICEATM announces the availability of revised analyses for four in vitro test methods proposed for detecting ocular corrosives and severe irritants [the Bovine Corneal Opacity and Permeability (BCOP) assay, the Hen's Egg Test—Chorion Allantoic Membrane (HET–CAM), the Isolated Rabbit Eye (IRE) assay, and the Isolated Chicken Eye (ICE) assay]. A revised list of proposed reference substances for validation studies on *in vitro* test methods for identifying ocular corrosives and severe irritants is also available. The revised analyses and list of proposed reference substances are provided in an addendum that is applicable to each of four draft Background Review Documents (BRDs) that were released to the public on November 3, 2004. The NICEATM invites public comment on the information provided in this addendum. Copies of the draft BRDs and addendum may be obtained on the ICCVAM/NICEATM Web site (*http://iccvam.niehs.nih.gov* see "Reports & Background Documents"), or by contacting NICEATM at the address given below.

DATES: Written comments and additional information should be received by August 25, 2005.

ADDRESSES: Comments and additional information should be sent by mail, fax, or e-mail to Dr. Raymond Tice, at NICEATM, NIEHS, P. O. Box 12233, MD EC–17, Research Triangle Park, NC 27709, (phone) 919–541–4482, (fax) 919–541–0947, (e-mail) *niceatmcomments@niehs.nih.gov*. Courier address: NICEATM, 79 T.W. Alexander Drive, Building 4401, Room 3113, Research Triangle Park, NC 27709

SUPPLEMENTARY INFORMATION:

Background

On November 3, 2004, NICEATM released draft BRDs that provided information about the current validation status of four *in vitro* test methods for detecting ocular corrosives and severe irritants (**Federal Register**, Vol. 69, No. 212, pp. 64081–64082, November 3, 2004, available at *http://iccvam.niehs.nih.gov/* see "Reports & Background Documents"). The test methods are the BCOP assay, the HET-CAM assay, the IRE assay, and the ICE assay. NICEATM in conjunction with ICCVAM convened an expert panel meeting on January 11–12, 2005, to independently assess the validation status of the four *in vitro* test methods. The expert panel report is available electronically at *http://iccvam.niehs.nih.gov/methods/eyeirrit.htm*. Public comments at the meeting indicated that additional data could be made available that had not been provided in response to earlier requests for data announced in the **Federal Register** in March and November 2004 (Vol. 69, No. 212, pp. 64081–64082, November 3, 2004; Vol. 69, No. 57, pp. 13859–13861, March 24, 2004). The expert panel recommended that NICEATM conduct a reanalysis of the accuracy and reliability of each test method that would include these data. In response to this recommendation, NICEATM published a notice in the **Federal Register** (Vol. 70, No. 38, pp. 9661–9662, February 28, 2005) requesting additional *in vitro* data on these four *in vitro* ocular irritancy test methods, corresponding *in vivo* rabbit eye test method data, as well as any human ocular exposure/injury data (either from ethical human studies or accidental exposure). In response to this request, NICEATM received additional *in vitro* and *in vivo* data that were used for the revised analyses and considered in revising the list of proposed reference substances.

The revised analyses and list of proposed reference substances are provided in an addendum that is applicable to each of four draft BRDs that were released to the public on November 3, 2004 (available at *http://iccvam.niehs.nih.gov/* see "Reports & Background Documents"). Following the public comment period, NICEATM in coordination with ICCVAM plans to reconvene the expert panel during a public teleconference to comment on the proposed reference substances and finalize their conclusions regarding the current validation status of the four methods for detecting ocular corrosives and severe irritants. The date and time for this teleconference will be announced in a future **Federal Register** announcement.

Request for Comments

NICEATM invites the submission of written comments on the revised analyses and the proposed list of reference substances. When submitting written comments please include appropriate contact information (name, affiliation, mailing address, phone, fax, email and sponsoring organization, if applicable). All written comments received by the deadline listed above will be posted on the ICCVAM/NICEATM website and made available to the expert panel and ICCVAM.

Background Information on ICCVAM and NICEATM

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, and replace animal use. The ICCVAM Authorization Act of 2000 (Pub. L. 106–545, available at *http://iccvam.niehs.nih.gov/about/PL106545.htm*) establishes ICCVAM as a permanent interagency committee of the NIEHS under the NICEATM. NICEATM administers the 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 following Web site: *http://www.iccvam.niehs.nih.gov*.

Dated: July 13, 2005.

David A. Schwartz,

Director, National Institute of Environmental Health Sciences and National Toxicology Program.

[FR Doc. 05–14707 Filed 7–25–05; 8:45 am]

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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); Announcement of Expert Panel Meeting To Evaluate Revised Analyses and Proposed Reference Substances for In Vitro Test Methods for Identifying Ocular Corrosives and Severe Irritants

AGENCY: National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH), Department of Health and Human Services (HHS).

ACTION: Meeting announcement and opportunity for public comment.

SUMMARY: NICEATM announces a second meeting of an expert panel by teleconference on September 19, 2005, to evaluate (1) revised accuracy and reliability analyses of four *in vitro* test methods proposed for detecting ocular corrosives and severe irritants and (2) a revised list of proposed reference substances for validation studies on *in vitro* test methods for identifying ocular corrosives and severe irritants. The four *in vitro* test methods under consideration are the (1) Bovine Corneal Opacity and Permeability (BCOP) assay, (2) Hen's Egg Test—Chorion Allantoic Membrane (HET–CAM), (3) Isolated Rabbit Eye (IRE) assay, and (4) Isolated Chicken Eye (ICE) assay. The revised analyses and revised list of proposed reference substances are available in an addendum to the draft Background Review Documents (BRDs) for the four methods (available at *http://iccvam.niehs.nih.gov/methods/ocudocs/reanalysis.htm*). A previous **Federal Register** notice solicited public comment on the revised analyses and revised list of proposed reference substances (Vol. 70, No. 142, pg. 43149, July 26, 2005). Comments submitted in response to the July 26, 2005 **Federal Register** notice will be considered at the expert panel meeting and do not need to be resubmitted. The public is invited to attend the teleconference and will be provided with an opportunity to make oral comments during the public comment period. Interested individuals can attend the meeting via a phone line or in person at the NIEHS campus (see **ADDRESSES** below). Participation is limited only by the number of phone lines available and by the number of available seats at the teleconference site. Additional meeting information may be obtained on the ICCVAM/NICEATM Web site (*http://iccvam.niehs.nih.gov*) or by contacting NICEATM (see **ADDRESSES** below).

DATES: The expert panel meeting will be held via teleconference on Monday, September 19, 2005, beginning at 9 a.m. eastern daylight time (e.d.t.) and continuing until adjournment (approximately 12 p.m. e.d.t.).

Requests to attend the meeting via the telephone or in person must be received no later than September 12, 2005, to ensure access (see **ADDRESSES** below). We encourage all individuals who plan to attend this meeting to register online at the NICEATM Web site (*http://iccvam.niehs.nih.gov/*), but requests may also be submitted by e-mail, telephone, fax, or through hand delivery/courier (see **ADDRESSES** below).

Persons wishing to make oral comments during the teleconference must notify NICEATM no later than September 12, 2005 (see **ADDRESSES** below). In lieu of oral comments, individuals may provide written comments for distribution to the expert panel prior to the meeting. Written comments should be received by September 15, 2005, in order to enable consideration by the expert panel prior to the meeting.

Persons with disabilities, such as those who need sign language interpreters and/or other reasonable accommodation to participate in this meeting at NIEHS, are asked to notify NICEATM by September 8, 2005.

ADDRESSES: The teleconference will originate from Room 3162, 3rd Floor, NIEHS, 79 T.W. Alexander Drive, Bldg. 4401, Research Triangle Park, NC. A government-approved photo ID is required to access the meeting.

Correspondence should be sent by mail, fax, e-mail, or through hand delivery/courier to Dr. Raymond Tice at NICEATM, NIEHS, PO Box 12233, MD EC–17, Research Triangle Park, NC 27709, (phone) 919–541–4482, (fax) 919–541–0947, (e-mail) *niceatmcomments@niehs.nih.gov*. Courier address: NICEATM, 79 T.W. Alexander Drive, Building 4401, Room 3129, Research Triangle Park, NC 27709.

SUPPLEMENTARY INFORMATION:

Background

On November 3, 2004, NICEATM released draft BRDs that provided information about the current validation status of the four *in vitro* test methods for detecting ocular corrosives and severe irritants (**Federal Register**, Vol. 69, No. 212, pp. 64081–64082, November 3, 2004). In conjunction with ICCVAM, NICEATM convened an expert panel meeting on January 11–12, 2005, to independently assess the validation status of the four *in vitro* test methods. The expert panel report and background information for this meeting are available at *http://iccvam.niehs.nih.gov/methods/eyeirrit.htm*. Public comments at the meeting indicated that additional data could be made available that had not been provided in response to earlier requests for data announced in the **Federal Register** in March (Vol. 69, No. 57, pp. 13859–13861, March 24, 2004) and November 2004). The expert panel recommended that NICEATM conduct a reanalysis of the accuracy and reliability of each test method that would include these data. In response to this recommendation, NICEATM published a notice in the **Federal Register** (Vol. 70, No. 38, pp. 9661–9662, February 28, 2005) requesting additional *in vitro* data on these four *in vitro* ocular irritancy test methods, corresponding *in vivo* rabbit eye test method data, as well as any human ocular exposure/injury data (either from ethical human studies or accidental exposure). Subsequently, NICEATM received additional *in vitro* and *in vivo* data that were used for the

revised accuracy and reliability analyses and considered in revising the list of proposed reference substances.

In preparation for this teleconference, NICEATM released the revised accuracy and reliability analyses and the revised list of proposed reference substances as an addendum to the draft BRDs and announced its availability in the July 26, 2006 **Federal Register** notice. Following the expert panel teleconference, a second expert panel report will be published and made available for public comment. ICCVAM will consider both expert panel reports, other relevant background materials, and all comments received from the public and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) on this topic in finalizing ICCVAM recommendations for these test methods.

Opportunity for Public Comment

Public comments may be made on the revised accuracy and reliability analyses for BCOP, HET–CAM, ICE, and IRE and on the proposed list of reference substances. In lieu of oral comments, individuals may provide written comments for distribution to the expert panel prior to the meeting. Written comments should be received no later than September 15, 2005, to enable consideration by the expert panel prior to the meeting. Written comments received in response to the July 26, 2005 **Federal Register** notice announcing availability of the addendum to the draft BRDs do not need to be resubmitted. If written comments are submitted, appropriate contact information (name, affiliation, mailing address, phone, fax, email and sponsoring organization, if applicable) should be included. Written comments will be posted on the NICEATM/ICCVAM Web site and made available to the expert panel and the ICCVAM. Persons wishing to make oral comments during the teleconference (one speaker per organization) must notify NICEATM by no later than September 12, 2005. Speakers will be assigned on a consecutive basis and comments will be limited to no more than four minutes per speaker. Due to logistical issues it may not be possible for persons who do not pre-register to make oral comments.

Background Information on ICCVAM and NICEATM

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, and replace animal use. The ICCVAM Authorization Act of 2000 (Pub. L. 106–545, available at *http://iccvam.niehs.nih.gov/about/PL106545.htm*) establishes ICCVAM as a permanent interagency committee of the NIEHS under the NICEATM. NICEATM administers the 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 following Web site: *http://www.iccvam.niehs.nih.gov.*

Dated: August 30, 2005.

Samuel H. Wilson,

Deputy Director, National Institute of Environmental Health Sciences.

[FR Doc. 05–17939 Filed 9–8–05; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Toxicology Program (NTP), NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Availability of a Second Expert Panel Request on the Evaluation of the Current Validation Status of In Vitro Test Methods for Identifying Ocular Corrosives and Severe Irritants

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

ACTION: Report availability and request for comments.

SUMMARY: NICEATM announces availability of the report "The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Expert Panel Evaluation of the draft Background Review Document Addendum for In Vitro Test Methods For Identifying Ocular Corrosives And Severe Irritants." NICEATM invites public comment on the expert panel report. Copies of the expert 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: Comments should be sent by mail, fax, or e-mail to the address given below by December 2, 2005.

FOR FURTHER INFORMATION CONTACT: Dr. Raymond Tice at NICEATM, NIEHS, P.O. Box 12233, MD EC–17, Research Triangle Park, NC, 27709, (phone) 919–541–4482, (fax) 919–541–0947, (e-mail) *niceatm@niehs.nih.gov*.

SUPPLEMENTARY INFORMATION:

Background

On November 3, 2004, NICEATM released draft background review documents (BRDs) that provided information about the current validation status of four in vitro test methods for detecting ocular corrosives and severe irritants (**Federal Register**, Vol. 69, No. 212, pp. 64081–64082, November 3, 2004). In conjunction with ICCVAM, NICEATM convened an expert panel meeting on January 11–12, 2005, to independently assess the validation status of the four in vitro test methods. The expert panel report from the January 2005 meeting ("first expert panel report") was released in March 2005 and is available at *http://iccvam.niehs.nih.gov/methods/eyeirrit.htm*. Public comments at the meeting indicated that additional data could be made available that had not been provided in response to earlier requests for data announced in the **Federal Register** in March (Vol. 69, No. 57, pp. 13859–13861, March 24, 2004) and November 2004. The expert panel recommended that NICEATM conduct a reanalysis of the accuracy and reliability of each test method that would include these data. In response to this recommendation, NICEATM published a notice in the **Federal Register** (Vol. 70, No. 38, pp. 9661–9662, February 28, 2005) requesting additional in vitro data on these four in vitro ocular irritancy test methods, corresponding in vivo rabbit eye test method data, as well as any human ocular exposure/injury data (either from human studies or accidental exposure). Subsequently, NICEATM received additional in vitro and in vivo data that were used for the revised accuracy and reliability analyses and considered in revising the list of proposed reference substances.

NICEATM released the revised accuracy and reliability analyses and the revised list of proposed reference substances as an addendum to the draft BRDs and announced its availability in the **Federal Register** (Vol. 70, No. 142, pg. 43149, July 26, 2005). NICEATM subsequently announced a second meeting of an expert panel by teleconference on September 19, 2005 in the **Federal Register** (Vol. 70, No. 174, pg. 53676, September 9, 2005). The second expert panel report is a product of the teleconference meeting and is being made available for public comment. ICCVAM will consider the first and second expert panel reports, other relevant background materials, and all comments received from the public and the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) on this topic in finalizing ICCVAM test method recommendations for these methods.

Request for Comments

NICEATM invites the submission of written comments on the second expert panel report. When submitting written comments please include appropriate contact information (name, affiliation, mailing address, phone, fax, e-mail and sponsoring organization, if applicable). All written comments received by the deadline listed above will be posted on the ICCVAM/NICEATM Web site and made available to ICCVAM agency representatives for their consideration prior to the development of final ICCVAM recommendations on these test methods.

An ICCVAM test method evaluation report, which includes the ICCVAM test method recommendations, will be forwarded to appropriate Federal agencies for their consideration. This report also will be available to the public on the ICCVAM/NICEATM Web site and by request to NICEATM.

Background Information on ICCVAM and NICEATM

ICCVAM is an interagency committee composed of representatives from fifteen Federal regulatory and research agencies that use or gerate 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 (Pub. L. 106–545, available at *http://iccvam.niehs.nih.gov/about/PLI06545.htm*) establishes ICCVAM as a permanent interagency committee of the NIEHS under the NICEATM. NICEATM administers the 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 following Web site: *http://www.iccvam.niehs.nih.gov*.

Dated: October 25, 2005.

Samuel H. Wilson,

Deputy Director, National Institute of Environmental Health Sciences.

[FR Doc. 05–21830 Filed 11–1–05; 8:45 am]

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APPENDIX I2
ICCVAM CONSIDERATION OF PUBLIC COMMENTS RECEIVED IN RESPONSE TO *FEDERAL REGISTER* NOTICES

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In response to six *Federal Register* (*FR*) notices that were released between March 2004 and July 2005, 149 public comments were received. Comments received in response to the *FR* notices and/or were related to those *FR* notices can be obtained on CD ROM upon request to NICEATM by mail, fax, or email (NICEATM, NIEHS, P.O. Box 12233, MD EC-17, Research Triangle Park, NC 27709, (phone) 919-541-2384, (fax) 919-541-0947, (email) niceatm@niehs.nih.gov). The following sections, delineated by *FR* notice, provide a brief discussion of the public comments received.

1.0 Public Comments Received in Response to *FR* Notice Released on March 24, 2004 (Volume 69, Number 57; pages 13859-13861)

NICEATM, in an *FR* notice (69 *FR* 57:13859-13861, March 24, 2004) requested (1) public comment on four test methods for ocular toxicity and related activities nominated to the ICCVAM by the EPA, (2) public comment on ICCVAM's recommended actions for the nomination, and (3) data from completed studies on chemicals and products tested for ocular irritancy using *in vitro* and/or *in vivo* test methods.

While no comments were received in response to this *FR* notice, on the four test methods or on ICCVAM's recommended actions for the nomination, NICEATM did receive submissions of data from:

- Access Business Group
- The Cosmetic, Toiletry, and Fragrance Association (CTFA)
- The European Centre for the Validation of Alternative Methods (ECVAM)
- ExxonMobil Biomedical Sciences, Inc.
- The German Center for Documentation and Evaluation of Alternative Methods to Animal Experiments (ZEBET)
- GlaxoSmithKline
- The Institute for In Vitro Sciences, Inc.
- The Japanese National Institute of Health Sciences
- L'Oréal
- Merck & Co., Inc.
- The Netherlands Organization for Applied Scientific Research (TNO) Nutrition and Food Institute
- The Procter & Gamble Company
- S.C. Johnson & Son, Inc./Johnson Diversey, Inc.
- The U.S. Food and Drug Administration

2.0 Public Comments Received in Response to *FR* Notices Released on November 3, 2004 (Volume 69, Number 212; pages 64081-64082) and December 3, 2004 (Volume 69, Number 232; pages 70268-70269)

In response to these *FR* notices, 61 comments were received on the four test method BRDs and the HET-CAM test method addendum.

All comments related to errors in the text and/or omissions of data were addressed in the final BRD for each test method. Additional information related to test method protocol

components and data analyses also was incorporated into the appropriate BRDs. Comments related to test method rationale, benefits and limitations of an *in vitro* test method and/or the *in vivo* rabbit eye test, proposed literature references for inclusion in the BRDs, and use of test methods protocols, decision criteria, and analyses in laboratories were fully reviewed and incorporated, as appropriate, into the final BRDs.

Of the comments received, 51 comments were related to requests that ICCVAM accept these test methods as replacements for the *in vivo* rabbit test and that there be no call for confirmatory testing (similar to the EU). ICCVAM agrees that some countries in the EU do accept a positive response in these test methods for classification purposes. However, ICCVAM notes that the European Chemicals Bureau has stated in July 2004:

> Although these tests [IRE, ICE, BCOP, HET-CAM] <u>are not yet validated</u> (and therefore not included in Annex V) it has been agreed that available evidence is sufficient to conclude that the methods are able to detect severe eye irritants. … Where a negative result is obtained, an *in vivo* test should subsequently be required, as the *in vitro* tests have not been shown to adequately discriminate between eye irritants and non-irritants. (emphasis added)

ICCVAM also appreciates the comments regarding acceptance of the test methods. It should be noted that it does not determine whether a test method or classification scheme is acceptable for use by U.S. Federal agencies or the international regulatory community. ICCVAM develops and forwards recommendations on the usefulness and limitations of the proposed test methods to each U.S. Federal agency for its review. Based on their specific statutory mandates, each U.S. Federal agency will consider ICCVAM's recommendations and then make a determination as to the acceptability of the test methods.

With respect to the issue of further validation efforts and the need for *in vivo* animal data, ICCVAM encourages the use of historical data, when available, to avoid further animal use.

Several comments focused on submitted data that were not used for the BRD analysis. ICCVAM and NICEATM appreciate all efforts made to provide data for the evaluation. However, specific criteria were established for inclusion of data in the BRD and/or the analysis conducted therein. When submitted data did not meet these criteria, they were excluded from the analysis. Also, the current evaluation did not focus on replacing the current method; rather, it focused on determining whether these methods could be used as part of a tiered-testing strategy to identify severe irritants <u>before</u> the test substance is evaluated in a rabbit.

Several comments related to the data collection and opportunities to increase data submission to NICEATM and ICCVAM were submitted. ICCVAM appreciates comments related to these processes and continuously strives to improve the process used in reviewing new alternative test methods. These constructive comments will be incorporated into this ongoing process as appropriate.

ICCVAM received comments concerning the replacement of the word *relevance* with the word *accuracy* in the definition of *validation* used in the BRDs. After reviewing these comments, ICCVAM acknowledges that the definition of *validation* contained in the *ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods (2003)* is in error and that this definition will be corrected in the final BRDs.

ICCVAM received comments that took issue with the approach to evaluate each test method individually rather than as part of a test battery, along with comments proposing additional methods. The initial nomination of the four evaluated test methods requests that the four test methods be evaluated individually. ICCVAM appreciates the proposal to evaluate the methods as a part of a battery and future evaluation of all or some of these methods as part of an ocular toxicity test battery may be considered.

ICCVAM received a comment that the protocol for the BCOP test outlined in the BRD cannot be validated using the recommended holder for the corneas, and proposed that an alternate holder be employed. ICCVAM also received comments that outlined how the use of histology as an additional endpoint in the BCOP test might improve its accuracy. ICCVAM appreciates any suggestions related to the optimization of test method protocols, and all comments were taken under consideration in the development of the final BRDs.

3.0 Public Comments Received in Response to *FR* Notice Released on February 28, 2005 (Volume 70, Number 38; pages 9661-9662)

NICEATM, in a *FR* notice (70 *FR* 38:9661-9662,February 28, 2005), made a second request for data from completed studies on chemicals and products tested for ocular irritancy using *in vitro* and/or *in vivo* test methods.

In response to this *FR* notice, NICEATM received three submissions of data. Data were received from:

- The TNO Nutrition and Food Institute
- Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
- ZEBET

ICCVAM and NICEATM gratefully acknowledge all the efforts made in obtaining and providing these data for this evaluation.

4.0 Responses to *FR* Notice released on March 21, 2005 (Volume 70, Number 53; pages 13513-13514)

NICEATM, in an *FR* notice (70 *FR* 53:13513-13514, March 21, 2005), requested submission of written comments on the report entitled "The Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Expert Panel Evaluation of the Current Validation Status of *In Vitro* Test Methods for Identifying Ocular Corrosives and Severe Irritants."

In response to the *FR* notice, 85 comments were received on the report. All comments related to errors in the text and/or omissions of data were addressed in the final BRD of each test method. Additional background information related to test method protocol components; data sources; test method rationale; benefits and limitations of an *in vitro* test method and/or the *in vivo* rabbit eye test; proposed literature references for inclusion in the BRDs; proposed sources of additional *in vivo* and human ocular toxicity data; and use of test methods protocols, decision criteria, and analyses in individual laboratories were fully reviewed and incorporated, as appropriate, into the final BRDs.

Eighty-one comments focused on requesting that U.S. Federal agencies begin accepting alternative test methods that are found to be useful and requested that recommendations made by the Expert Panel directed at improving alternative test these methods not delay the acceptance of their current forms. ICCVAM appreciates the comments regarding acceptance of the test methods. ICCVAM notes that each U.S. Federal Agency makes the ultimate determination on whether a test method is acceptable for use. However, ICCVAM will develop and forward recommendations on the usefulness and limitations of the proposed test methods to each U.S. Federal agency for their review. Based on their specific statutory mandates, each Federal agency will then make a determination on the acceptability of the test methods.

Several comments were either (1) general responses to comments made by the Expert Panel in the report or (2) questions posed in response to the Expert Panel Report. All such comments were reviewed by ICCVAM and NICEATM. ICCVAM appreciates these comments and they were considered during the development of the ICCVAM recommendations.

Several comments related to the data collection and Expert Panel processes were submitted. Comments agreed with the Minority Opinions presented in Section 12.2 of the BCOP Expert Panel report. Comments also proposed additional methods and proposed opportunities to increase data submission to NICEATM and ICCVAM (e.g., provide corporate confidentiality). Comments related to these processes were appreciated as ICCVAM continuously strives to improve the process used in reviewing new alternative test methods. These constructive comments will be incorporated into this ongoing process, as appropriate.

One comment stated that the BRD should address the public comments that are submitted, including those provided by the supplier of the data cited. The comments proposed that inaccuracies and/or confusions about data sets should be clarified prior to finalization of the BRD for use by the Expert Panel. As a point of clarification, the BRDs used by the Expert Panel during their review of the documents were in draft, and not final, form. Additionally, all public comments on the BRDs were provided to the Expert Panel for their review and information prior to the Expert Panel meeting on January 11-12, 2005. This allowed the Expert Panel to review and request additional information, as needed, from NICEATM.

Several comments agreed with the Expert Panel's conclusion that additional information and discussion were needed in the BRDs about the accuracy and reliability of the *in vivo* test method and that variability of the *in vivo* test should be considered when comparing *in*

vivo/*in vitro* data. Additional discussion on this topic has been incorporated into Section 4.0 of each BRD.

Several comments focused on submitted data that was not used by NICEATM for the BRD analysis or was repeatedly used "incorrectly". ICCVAM and NICEATM appreciate all efforts made to provide data for the evaluation. However, it is noted that in order to conduct the evaluation (i.e., assess the ability of the nominated test methods to identify severe irritants and ocular corrosives, as classified by regulatory classification systems), specific criteria must be met prior to inclusion of the data in the BRD and/or the analysis conducted therein (see Section 4.0 of each BRD). Therefore, some data received (e.g., *in vitro* data compared to benchmark controls, *in vivo* MAS data) could not be included in the accuracy analyses because it did not meet these minimum requirements. Data provided by individuals and companies that were not used in the BRD analyses were discussed in Section 9.0 of the relevant BRD or as Appendices to the BRDs. For those data that were used "incorrectly", all errors and omissions have been corrected in the final BRD.

ICCVAM received comments concerning the replacement of the word *relevance* with the word *accuracy* in the definition of *validation* used in the BRDs. As previously noted, after reviewing these comments, ICCVAM acknowledges that the definition of *validation* contained in the *ICCVAM Guidelines for the Nomination and Submission of New, Revised, and Alternative Test Methods (2003)* is in error and that references to this definition will be corrected in the final BRDs.

Comments were received related to the potential inclusion of histopathology as an endpoint for some of the organotypic test methods. As previously indicated in public forum, ICCVAM would be very interested in identifying formal decision criteria for this endpoint that would allow for its standardized use, and would welcome any available histopathology data that are generated during studies with any of these test methods.

A comment was submitted stating that Low Volume Eye Test (LVET) more highly correlated to the human response than the *in vivo* rabbit eye test. The comment stated that the *in vivo* rabbit eye test has been documented to overpredict the human response, but the degree of overprediction was unknown. The comment stated that overprediction did not equal scientific credibility, a feature being strived for in replacing the current whole animal method. ICCVAM appreciates the comments provided, but notes that the current evaluation was not focused on replacing the current method. This evaluation was focused on determining whether these methods could be used, as part of a tiered-testing strategy, to identify severe irritants before the test substance is evaluated in a rabbit. ICCVAM also notes that LVET data was used in the accuracy evaluation, if there was corresponding *in vitro* data, and when a severe response was observed in the rabbit.

Some comments were submitted that focused on the comparison made in the BRDs and by the Expert Panel on the cost of the *in vitro* and *in vivo* studies. The comments suggest that such a comparison, as well as a comparison of time needed to conduct the studies, is complicated. ICCVAM appreciates the concerns raised by the commentors. However, it is noted that an evaluation of the practical considerations of the test method (e.g., transferability

of the test method, cost of the method) is incorporated into the ICCVAM evaluation process. While ICCVAM does not use the cost and time to complete the *in vitro* test, when compared to the reference *in vivo* test, as the main factor in evaluating alternative test methods, these considerations are evaluated together with the accuracy and the reliability when establishing the regulatory utility of an alternative method.

5.0 Public Comments Received in Response to *FR* Notice Released on July 26, 2005 (Volume 70, Number 142; page 43149)

In response to this *FR* notice, three comments were received on the revised analyses for the four test method BRDs. All comments related to errors in the text and/or omissions were incorporated into the final BRD. All comments related to proposed analyses have been reviewed and incorporated, where appropriate and practical.

One comment submitted was the concern of correlating *in vitro* results with the EPA ocular hazard classification system, given that a single animal can lead to a severe classification regardless of the results in any other tested animals. Until the GHS classification system is formally adopted, all relevant hazard classification systems (i.e., those used by the U.S. EPA, the European Union [EU], and the GHS) must be considered when determining the utility of an *in vitro* test method for hazard identification. Therefore, ICCVAM believes that an evaluation against the EPA hazard classification system is appropriate.

A comment also noted that there are instances in which different hazard classifications are assigned to the same substance depending on the ocular hazard classification system used (i.e., EPA, EU, GHS), due to the differences in weighting assigned to the same data among the different classification systems. However, the analyses demonstrate that the accuracy of an individual *in vitro* test method is largely independent of which classification system is considered, suggesting that these differences are small.

Two comments were submitted relating to the criteria for acceptance of hazard classification information for test substances evaluated in the *in vitro* test methods. These comments focused on the exclusion of substances from the analyses, based on a lack of adequate *in vivo* rabbit data. While *in vivo* dermal corrosive effects (or extremes of pH) are utilized in ocular hazard classification systems as substitutes for *in vivo* rabbit eye test results for the purposes of ocular hazard classification, the goal of this assessment is to evaluate the accuracy of four *in vitro* test methods for identifying ocular corrosives and severe irritants, as determined by the *in vivo* rabbit eye test. Therefore, substances that lacked *in vivo* rabbit eye test results were excluded from the evaluation. However, to the extent such studies could be identified, data derived from scientifically acceptable *in vivo* rabbit eye tests terminated early based on humane endpoints were included in the accuracy and reliability analysis.