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.

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

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.

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