



National Institutes of Health
National Institute of
Environmental Health Sciences
NTP Interagency Center for the Evaluation
of Alternative Toxicological Methods
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MEMORANDUM

DATE: January 14, 2011

TO: The Interagency Coordinating Committee on the Validation of Alternative Methods

FROM: Director, National Institute of Environmental Health Sciences and the National Toxicology Program

SUBJECT: NIEHS Response to ICCVAM Test Recommendations for Ocular Safety Testing

On September 2, 2010, at the request of the Secretary of the Department of Health and Human Services, I forwarded toxicological test recommendations from the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) to 14 Federal agencies for their consideration. The recommendations were developed and transmitted pursuant to Section 3(e)(4) of the ICCVAM Authorization Act of 2000 (42 U.S.C. 285l-3). Pursuant to Sections 4(a) and 4(d) of the ICCVAM Authorization Act, agencies are required to review ICCVAM test recommendations and notify ICCVAM in writing of their findings, including identification of relevant test methods for which the ICCVAM test recommendations may be added or substituted. This memorandum provides the NIEHS response to ICCVAM regarding the test method recommendations.

ICCVAM provided recommendations on alternative testing methods and strategies proposed to further reduce and refine the use of animals for assessing the ocular hazard potential of chemicals and products. The recommendations were provided in four ICCVAM test method evaluation reports that included detailed data analyses and conclusions supporting the recommendations.

NIEHS agrees with the ICCVAM recommendation that pain management procedures should always be used when it is determined necessary to conduct the rabbit eye safety test, and agrees with the recommended procedures for the use of topical anesthetics, systemic analgesics, and earlier humane endpoints. Routine use of these procedures should effectively eliminate pain and distress whenever it is determined necessary to use animals for ocular safety testing. NIEHS applauds ICCVAM for this significant contribution to improved animal welfare.

NIEHS agrees with the ICCVAM recommendation that the accuracy and reliability of the Cytosensor Microphysiometer (CM) test method supports its use as a screening test to identify some specific types of substances that will not cause sufficient injury to require labeling as a potential eye hazard. The availability of this and future *in vitro* methods that can be used to make regulatory safety decisions that a substance is not a hazard for a specific type of toxicity can be expected to

significantly reduce the number of animals used in ocular and other types of safety testing. NIEHS also agrees with the ICCVAM recommendation that CM can be used as a screening test to identify some categories of substances that may cause permanent or severe eye injuries.

NIEHS agrees with the ICCVAM recommendation that the accuracy and reliability of four other *in vitro* test methods do not support their use for identifying substances that cause reversible and nonsevere ocular injuries or substances that do not require labeling as eye hazards. NIEHS agrees that, as required by the ICCVAM Authorization Act, the methods must provide data that is at least equivalent to the data generated from existing tests for hazard identification or risk assessment purposes. NIEHS also agrees that the proposed non-animal testing strategy using three *in vitro* test methods does not have adequate predictivity for regulatory hazard identification purposes. However, NIEHS supports the ICCVAM recommendations for future studies that could potentially improve these test methods and the testing strategy, and encourages such studies by interested stakeholders as well as future ICCVAM evaluation of improved methods and strategies.

NIEHS agrees with the ICCVAM recommendation that a proposed low volume rabbit eye test should not be used for regulatory testing due to performance issues when compared to the current standard rabbit eye test.

NIEHS is concerned by the ICCVAM finding that an estimated 30% of substances classified as eye hazards by current U.S. regulations are not classified as eye hazards using the United Nations Globally Harmonized System for Classification and Labelling of Chemicals (GHS). This concern is heightened by the fact that over half of the substances not classified as eye hazards by GHS caused corneal and/or internal eye injuries that could be expected to interfere with normal vision. NIEHS is aware that GHS is currently under consideration for implementation by the Occupational Safety and Health Administration and other Federal agencies. NIEHS therefore agrees with the ICCVAM recommendation that U.S. agencies should be aware of and consider the significant reduction in eye hazard labeling that will result from using the GHS compared to current U.S. eye hazard classification criteria. NIEHS supports the proposal in the ICCVAM evaluation report for consideration of an optional GHS category that could be used to avoid reduced hazard labeling and that would support continued protection of workers and consumers at the level provided by current U.S. regulations. NIEHS suggests that ICCVAM could serve as an interagency forum for further technical evaluation of these issues and that ICCVAM together with the NTP Interagency Center for the Evaluation of Alternative Methods could provide technical and scientific support necessary to resolve the issues in a manner that could ensure that the current level of protection for U.S. consumers and workers is not reduced.

NIEHS is not a regulatory agency and therefore does not promulgate regulatory testing requirements or guidelines for which the ICCVAM recommendations may be applicable. While NIEHS does conduct toxicity testing as part of its National Toxicology Program activities, ocular safety testing is not normally performed. However, NIEHS and the NTP will promote and encourage use of the alternative testing methods and strategies to further reduce and refine the use of animals for assessing the ocular hazard potential of chemicals and products. Accordingly, NIEHS and NTP scientists and the NIEHS Institutional Animal Care and Use Committee (IACUC) have been informed about the availability of these test methods and strategies. They have also been advised that if eye safety testing studies are proposed, then these alternative test methods should be routinely considered and used where appropriate in order to avoid or minimize animal use, and to avoid pain and distress when it is necessary to use animals. To comply with the Public Health Service Policy on Humane Care and Use of Laboratory Animals and applicable USDA Animal Welfare Act Regulations, the NIEHS

IACUC has also been asked to ensure that these alternative methods are always considered whenever applicable and to ensure that the methods are used when determined appropriate.

NIEHS appreciates ICCVAM's comprehensive evaluations and recommendations for the use of new, revised, and alternative safety testing methods. NIEHS is pleased that ICCVAM continues to consistently provide objective and comprehensive evaluations that ensure that new test methods recommended by the committee will support equivalent or improved protection of consumers and workers.

NIEHS remains highly committed to the development, validation, and regulatory acceptance of scientifically sound alternative safety testing methods that will support improved protection of people, animals, and the environment while providing for improved animal welfare.

/s/

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.

cc:

Dr. John Bucher, Associate Director, NTP

Dr. William Stokes, Executive Director, ICCVAM

Dr. Jodie Kulpa-Eddy, Acting Chair, ICCVAM