Preface

In 1998, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) in conjunction with the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) evaluated the validation status of the murine local lymph node assay (traditional LLNA) as an alternative to guinea pig test methods (e.g., the Guinea Pig Maximization Test and the Buehler Test) for assessing the allergic contact dermatitis (ACD) potential of substances. ICCVAM subsequently recommended that the LLNA could be used as a valid substitute for the accepted guinea pig test methods in most ACD testing situations (ICCVAM 1999).

Based on the ICCVAM recommendations, the ICCVAM member agencies that require regulatory submission of ACD data accepted the LLNA, with identified limitations, as an alternative to guinea pig tests for assessing the potential of substances to cause ACD. In 2002, the LLNA was adopted as Test Guideline 429 by the 30 member countries of the Organisation for Economic Co-operation and Development (OECD; OECD 2002).

The reduced murine local lymph node assay (rLLNA), also referred to as the "cut-down" or "limit dose" LLNA, was one of several modified versions of the LLNA nominated by the U.S. Consumer Product Safety Commission (CPSC) for evaluation by ICCVAM.[30] (The term "reduced LLNA" has been adopted in this document to be consistent with the terminology used for this test method in Europe.) The proposed rLLNA could reduce the number of animals for skin sensitization testing by 40% for each test compared with the traditional LLNA. ICCVAM assigned this activity a high priority following consideration of comments from the public and ICCVAM's advisory committee, the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM).

The ICCVAM Immunotoxicity Working Group (IWG) and NICEATM (1) prepared a draft background review document (BRD) that described the validation status of the rLLNA test method, including its reliability and accuracy, the substances evaluated, and the availability of a standardized protocol and (2) developed draft test method recommendations based on this evaluation. An international independent scientific peer review panel (Panel) met on March 4–6, 2008, to assess the current validation status of the rLLNA. The Panel also reviewed the completeness and accuracy of the draft ICCVAM BRD and the extent to which the information therein supported the ICCVAM draft test method recommendations for proposed test method uses, recommended protocol, test method performance standards, and future studies.

ICCVAM considered the conclusions and recommendations of the Panel, as well as comments received from the public and SACATM, when finalizing ICCVAM's BRD and test method recommendations on the usefulness and limitations of the rLLNA.

We gratefully acknowledge the organizations and scientists who provided data and information for this BRD. We would also like to recognize the efforts of the individuals who contributed to its preparation, review, and revision. We especially recognize the Panel members for their thoughtful evaluations and generous contributions of time and effort. Special thanks are extended to Dr. Michael Luster for serving as the Panel Chair and to Dr. Michael Woolhiser, Dr. Michael Olson, and Ms. Kim Headrick for their service as Evaluation Group Chairs. We

[30] Available at http://iccvam.niehs.nih.gov/methods/immunotox/llnadocs/CPSC_LLNA_nom.pdf

thank the IWG for assuring a meaningful and comprehensive review. We especially thank Dr. Joanna Matheson (CPSC) and Dr. Abigail Jacobs (U.S. Food and Drug Administration Center for Drug Evaluation and Research) for serving as Co-Chairs of the IWG, as well as the IWG members and ICCVAM representatives who subsequently reviewed the BRD and provided comments.

Integrated Laboratory Systems, Inc., the NICEATM support contractor, provided excellent scientific and operational support for which we thank Dr. David Allen, Mr. Thomas Burns, Ms. Linda Litchfield, Mr. Michael Paris, Dr. Eleni Salicru, Ms. Catherine Sprankle, and Dr. Judy Strickland. We also acknowledge Dr. Raymond Tice, Deputy Director of NICEATM, for his contributions to this project. Finally, we want to thank Dr. Silvia Casati and Dr. Hajime Kojima, the IWG liaisons from the European Centre for the Validation of Alternative Methods and the Japanese Center for the Validation of Alternative Methods, respectively for their participation.

William S. Stokes, D.V.M., D.A.C.L.A.M.
Rear Admiral/Assistant Surgeon General, U.S. Public Heath Service
Director, NICEATM
Executive Director, ICCVAM

Marilyn Wind, Ph.D.
Deputy Associate Executive Director
Directorate for Health Sciences
U.S. Consumer Product Safety Commission
Chair, ICCVAM