Preface

Acute systemic toxicity testing is conducted to determine the relative health hazard of chemicals and various products. Substances found to cause lethality in animals at or below prescribed doses are labeled to identify their hazard potential. While acute toxicity testing is currently conducted using animals, studies published in recent years have shown a correlation between *in vitro* and *in vivo* acute toxicity. These studies suggest that *in vitro* methods may be helpful in predicting *in vivo* acute toxicity.

An International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity was convened on October 17-20, 2000, to review the validation status of available *in vitro* methods for predicting acute toxicity, and to develop recommendations for future research and development efforts that might further enhance the use of *in vitro* assessments of acute systemic toxicity. The Workshop was organized by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM). The U.S. Environmental Protection Agency (U.S. EPA), the NTP, and the National Institute of Environmental Health Sciences (NIEHS sponsored the workshop. Breakout Groups, comprised of invited scientific experts and ICCVAM agency scientists, developed conclusions and recommendations for four topics:

- *In Vitro* Screening Methods for Assessing Acute Toxicity;
- *In Vitro* Methods for Toxicokinetic Determinations;
- *In Vitro* Methods for Predicting Organ Specific Toxicity; and
- Chemical Data Sets for Validation of *In Vitro* Acute Toxicity Test Methods.

The Breakout Group that addressed the first topic, "*In Vitro* Screening Methods," was charged with evaluating the current validation status of basal cytotoxicity methods, and recommending whether and how these methods might be used to reduce and refine animal use for acute toxicity testing. The Group concluded that *in vitro* cytotoxicity data could be useful in estimating starting doses for *in vivo* acute toxicity testing, which will reduce the number of animals required for such determinations. Their conclusions were based on several studies but primarily those by Drs. Horst Spielmann and Willi Halle, and their colleagues at the German Centre for the Documentation and Evaluation of Alternatives to Testing in Animals. Halle compiled a Registry of Cytotoxicity containing *in vivo* acute toxicity data and *in vitro* cytotoxicity data for 347 chemicals. These data were used to construct a regression model to estimate LD_{50} values from cytotoxicity data. They subsequently proposed that using these estimates as starting doses for *in vivo* acute toxicity studies such as the Up-and-Down Procedure or the Acute Toxic Class method could reduce the number of animals used by as much as 30 percent. In addition, the Group recommended that this guidance document be prepared to provide practical guidance on how to generate and use basal cytotoxicity data to predict starting doses for *in vivo* acute toxicity assays. Drs. Manfred Liebsch, Rodger Curren, and Julia Fentem volunteered to draft this document and after the Workshop they worked with NICEATM to develop it. This guidance document has been reviewed by ICCVAM, the ICCVAM Workshop Organizing Committee, and those participating in the Breakout Group on *In Vitro* Screening Methods.

The workshop results have been published as the *Report on the International Workshop on In Vitro Methods for Assessing Acute Systemic Toxicity* (NIH Publication No. 01-4499). The Organizing Committee and ICCVAM developed test recommendations to forward with these publications to Federal agencies for their consideration in accordance with Public Law 106-545. The ICCVAM recommendations are provided in the Workshop Report. Both

publications are available at the ICCVAM/NICEATM website (http://iccvam.niehs.nih.gov), or a copy may be requested from NICEATM at P.O. Box 12233, MD EC-17, Research Triangle Park, NC 27709 (mail), 919-541-3398 (phone), 919-541-0947 (fax), or NICEATM@niehs.nih.gov (email).

On behalf of the ICCVAM, we gratefully acknowledge the efforts of the Breakout Group on *In Vitro* Screening Methods for their comprehensive evaluation of existing data and methods that served as the impetus for this guidance document. We extend our sincere appreciation to the contributing authors, Drs. Manfred Liebsch, Rodger Curren, and Julia Fentem, for their considerable efforts and contributions to this document. The efforts of the NICEATM staff in coordinating the preparation and publication of the document are acknowledged and appreciated, particularly those of Dr. Judy Strickland and Mr. Michael Paris, who worked diligently with the authors to produce the final version.

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