DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Date: September 9, 2003

To: The Record

From: Director, NIEHS

Subject: NIEHS Response to Test Recommendations on Acute Toxicity from the Interagency Coordinating Committee on the Validation of Alternative Methods

On March 21, 2003, 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 (P. L. 106-545). 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 the ICCVAM test recommendations.

NIEHS has reviewed the ICCVAM test recommendations that were provided for 1) the revised Up-and-Down Procedure (UDP) and 2) *in vitro* methods for estimating the starting dose for acute oral toxicity studies. NIEHS agrees that the UDP significantly reduces the number of animals required to estimate the median oral lethal dose of chemicals, and that the *in vitro* methods can be helpful in further reducing the number of animals required for such studies. NIEHS has determined that it does not currently use or specify any test methods for which the test recommendations may be added or substituted. Furthermore, NIEHS is not a regulatory agency, and therefore does not promulgate regulatory testing requirements for which the recommendations may be applicable. NIEHS does conduct toxicity testing as part of its National Toxicology Program activities; however, acute oral toxicity testing to estimate median lethal doses is not normally performed. If, for some unforeseen reason, such data are required in the future, the NIEHS intends to follow the recommendations of the ICCVAM on this matter and use the UDP and the *in vitro* methods where appropriate.

NIEHS scientists and the NIEHS Institutional Animal Care and Use Committee (IACUC) have been informed about the availability of these two alternative test methods and advised that they should be considered when planning and reviewing animal studies involving acute systemic toxicity in order to minimize animal use and to reduce pain and distress. The IACUC has also been asked to ensure that these alternative methods are considered in accordance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals and applicable USDA Animal Welfare Act regulations.

NIEHS has also reviewed the ICCVAM recommendations for research, development, and validation efforts that could advance the use of *in vitro* methods for assessing acute systemic toxicity. NIEHS through its National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) has initiated a validation study to standardize and evaluate the usefulness of two *in vitro* basal cytotoxicity assays for predicting starting doses for *in vivo* acute oral toxicity studies and for predicting lethal concentrations in humans. Expert scientists participating in the ICCVAM International Workshop on In Vitro Methods for Assessing Acute Systemic Toxicity recommended the study. The project is co-funded by the U.S. Environmental Protection Agency and is being conducted in collaboration with the European Commission's European Center for the Validation of Alternative Methods (ECVAM).

NIEHS remains committed to the development, validation, and regulatory acceptance of scientifically sound alternative testing methods that will provide improved protection of human and animal health and the environment, and that will provide for improved animal welfare.

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cc:
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