DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P. O. Box 12233
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MEMORANDUM

DATE: August 25, 2008

TO: The Record

FROM: Acting Director, NIEHS

SUBJECT: NIEHS Response to ICCVAM Recommendations on In Vitro Cytotoxicity Test Methods for Estimating Starting Doses for Acute Oral Systemic Toxicity Tests

On February 28, 2008, 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. 285*l*-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 the ICCVAM test recommendations.

NIEHS has reviewed the ICCVAM test method recommendations for two *in vitro* alternative test methods for estimating starting doses for acute oral systemic toxicity tests. NIEHS agrees that the test methods should always be considered before using animals for acute oral toxicity testing and that the methods should be used when determined appropriate. NIEHS also agrees that data from the test methods should be used in a weight-of-evidence approach for determining starting doses for *in vivo* studies and that use of the *in vitro* methods where appropriate is expected to reduce the number of animals required for each toxicity test. NIEHS agrees that the *in vitro* test methods are not sufficiently accurate to replace animals for regulatory hazard classification purposes.

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. While NIEHS does conduct toxicity testing as part of its National Toxicology Program activities, acute oral systemic toxicity testing 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 recommended *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 alternative test methods and advised that they should always be considered when planning and reviewing animal studies involving acute oral toxicity testing 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 whenever applicable 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 and agrees with the ICCVAM recommendations for future studies to improve the usefulness of *in vitro* assays for assessing acute oral systemic toxicity for regulatory hazard classification purposes. NIEHS, through its National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), will coordinate selected test method studies and activities identified as high priority by ICCVAM with the goal of increasing test method accuracy and expanding the applicability of the test methods. NICEATM has also created a comprehensive database of high quality *in vivo* reference data that can be used to select reference chemicals for future validation studies. NIEHS, through the NTP's Biomolecular Screening Branch is also generating large volumes of publicly available data using similar cytotoxicity assays. These data may also help to identify more predictive *in vitro* testing strategies. NICEATM will continue to update both the *in vivo* and *in vitro* acute toxicity databases as new data are received.

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

Samuel H. Wilson, M.D.

Attachment

cc:
Dr. William Stokes, Executive Director, ICCVAM
Dr. Marilyn Wind, Chair, ICCVAM