DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Agency for Toxic Substances
and Disease Registry
Atlanta GA 30333

August 25, 2003

Kenneth Olden, Ph.D.
Director
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, North Carolina 27709

Dear Dr. Olden:

This is a follow-up to our correspondence of May 5, 2003 regarding testing recommendations for 1) *In Vitro* methods that can be used to estimate starting doses for acute oral toxicity studies, and 2) a revised test method (Up-and-Down Procedure, [UDP]) for determining acute oral toxicity, that were prepared by the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and sent to the Agency for Toxic Substances and Disease Registry (ATSDR) pursuant to the ICCVAM Authorization Act of 2000. Specifically, ATSDR (and other agencies) is required to review the test recommendations and notify the ICCVAM in writing of their findings, including identification of relevant test methods for which the ICCVAM test recommendations may be added or substituted.

We have reviewed the "Report of the International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity" and the accompanying "Guidance Document on Using *In Vitro* Data to Estimate *In Vivo* starting Doses for Acute Oral Toxicity," and support the ICCVAM recommendations for additional research and development efforts that would further advance the usefulness of the *in vitro* methods. In particular, we look forward to reviewing the results of the ongoing collaborative validation study between the U.S. and the European Committee on the Validation of Alternative Methods (ECVAM) that would further corroborate the reliability and accuracy of these methods. As suggested in your letter, ATSDR will make information about this approach available as one of the tools that can be used to select an appropriate starting dose for acute toxicity tests.

The revised UDP was proposed as an alternative to the existing LD_{50} and brought to the ICCVAM to assess its validation status in 1999. We agree with the conclusions of the scientific peer review panel and the recommendations of the ICCVAM that the revised UDP does perform appropriately and will result in a reduction and refinement in animal usage compared to the conventional LD_{50} test (about 50 animals versus 7 animals). ATSDR is not a regulatory agency, but does have a mandate to assure the initiation of a toxicological program of research to fill research needs for the most hazardous substances found at waste sites, and to date we have identified 263 priority data needs for 60 substances. It is important to note, however, that ATSDR does not require LD_{50} data for this program, but that such data are

reported in ATSDR toxicological profiles and have possible relevance in emergency situations. Thus, we support the use of the scientifically valid revised UDP on grounds of reduction and refinement of the use of animals in research, but note that there are no ATSDR toxicological tests or test method recommendations that will be added or substituted as a result. Instead, the availability of the revised UDP as a valid test method to assess acute oral toxicity will be shared with ATSDR program staff and with various public and private sector partners who work closely with ATSDR in accomplishing its research and service missions.

In closing, we strongly support the goal of the ICCVAM to coordinate the validation of proposed new test methods throughout the federal and scientific communities. We find ourselves in a solid position to defend new test methods, such as the revised UDP, when we are assured that the methodology meets the validation criteria established by the ICCVAM and has passed the rigors of scientific peer review. We look forward with keen interest to your report on the acceptance status of the revised UDP method by the regulatory agencies. Please share this information as it becomes available.

Sincerely,

Henry Falk, M.D., M.P.H.
Assistant Administrator
Rear Admiral, U.S.P.H.S. (Retired)

cc:
Bill Cibulas, Division of Toxicology, ATSDR