Dr. William S. Stokes
Director,
National Toxicology Program Interagency Center for
Evaluation of Alternative Toxicological Methods (NICEATM)
National Institute of Environmental Health Science (NIEHS)
P.O. Box 12233, MD EC-17
Research Triangle Park, NC 27709

RE: Public comment regarding development of NICEATM/ICCVAM 5- Year Plan To Research, Develop, Translate, and Validate New and Revised Non-animal and Other Alternative Assays for Integration of Relevant and Reliable Methods Into Federal Agency Testing Programs; Federal Register: November 13, 2006, Volume 71, Number 218, Pages 66172-66173.

Dear Dr. Stokes:

The American Chemistry Council strongly supports the mission of the Interagency Coordinating Committee for Validation of Alternative Methods (ICCVAM). For over three decades the American Chemistry Council (ACC or the "Council") and its member companies have played an active role in both screening and testing chemical substances and in the development of alternative toxicity test methods.[1] Recognizing that responsible use of animals in research and testing will continue to be required to protect human and animal health and to safeguard the environment, when animal testing is necessary, the Council is firmly committed to minimizing the use of laboratory animals and is equally committed to conducting animal research in the most humane ways possible. At this time, science depends on the use of laboratory animal test methods to predict the effect a chemical may have on humans and other species. Animal testing is a way to collect scientifically valid information that domestic and international policy-makers, the public and manufacturers need to help ensure public health and safety. In the absence of human data, chemical research and testing with laboratory animals is the most reliable means of detecting toxic properties and for estimating risks to human health and the environment. In addition to large-scale research programs, chemical manufacturers are required by state and federal laws to test individual products. These investigations rely on validated, predictable, reliable test methods that are accepted by regulatory bodies, not on new and novel experimental methodologies that have yet to be shown to be relevant and reliable.

[1] The American Chemistry Council represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a $460 billion enterprise and a key element of the nation's economy. It is the nation's largest exporter, accounting for ten cents out of every dollar in U.S. exports. Chemistry companies invest more in research and development than any other business sector. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, working closely with government agencies to improve security and to defend against any threat to the nation's critical infrastructure.

ACC encourages the use of alternatives to animal testing when these alternatives are scientifically valid and predictive and acceptable to regulatory bodies. Since reliable alternatives to animal testing are not presently available for every type of toxicity testing now required, research to reduce, refine or replace the need for laboratory animals should continue. Alternative methods need to be proven as suitable replacements for currently accepted methods. They need to provide an appropriate level of understanding to address concerns for human health and the environment with an adequate degree of scientific certainty. Currently, some of the alternative methods provide limited information that is relevant to a very specific test condition but may not adequately predict results in a complicated organism such as humans. As new methods and techniques are developed and applied the Council will work collaboratively to reduce, refine and replace the use of animals.

With respect to the scope of the 5-Year Planning effort, we believe it is important for ICCVAM and the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) to go beyond simply seeking comment on a series of endpoints and assays focused on such endpoints. In particular, the ICCVAM/NICEATM 5-Year Planning effort should include consideration of these assays and endpoints within the context of their respective regulatory testing and evaluation batteries. Why is it important to look beyond the endpoints and the endpoint test methods and to look at the regulatory testing and evaluation batteries? Because it is only in looking at the batteries that specific focus can be applied to understand the uses of the test results in regulatory decision making. Each alternative method must be shown to be both relevant and reliable for its intended purpose. Since there are a multitude of potential uses of testing information, each with potentially different purposes and degrees of required certainty, it is only through examination of the test methods within the context of the battery that defines its regulatory use where one can understand the relevance of the testing results for the regulatory decision. Theoretically, regulatory approaches can accept greater uncertainty for some decisions, compared to others. Some approaches require quantitative evaluation, while others may be qualitative. Thus, new, revised and alternative test methods or batteries that utilize such methods may have applicability in certain regulatory decision making approaches and not in others, depending upon the degree of certainty required. Dose and exposure are important components and should not be overlooked.

In designing the process for developing the 5-Year Plan, ICCVAM/NICEATM should review the outcome of the 2005 Workshop "Progress and Barriers to Incorporating Alternative Toxicological Methods in the U.S." A summary of the Workshop has been published in *Regulatory Toxicology and Pharmacology*[2]. The recommendations of the Workshop include a specific call for "… a need to develop, evaluate and promote the use of integrated or tiered testing strategies (which incorporate scientifically based decision triggers that signal the need for additional testing) [and that [e]valuation should be capable of demonstrating that such approaches can provide sufficient data and certainty to support regulatory decision-making." Such tiered testing approaches are critically important to assure that results-based prioritization is employed to focus testing on chemicals of greatest concern to public health, thus reducing the total amount of testing and animal research necessary to protect public health. Furthermore, ACC supports using hazard *and* exposure data to prioritize substances for further evaluation, which provides more efficient use of resources, including laboratory animals. The HPV Challenge Program and the VCCEP Pilot Program are two-such tiered-testing and

[2] see pdf at
http://www.isrtp.org/nonmembers/Alternative%20Tox%20Methods%20Nov%202005/ELSEVIER%20PDF%20Becker%20et%20al%20%202006.pdf

evaluation programs that ACC has partnered in pioneering. Another example is the ILSI/HESI Agricultural Chemical Safety Assessment (ACSA) tiered approach, which incorporates existing knowledge on the chemistry, toxicology, and actual human exposure scenarios of the compound, with integration of studies on metabolism/kinetics, life stages, and systemic toxicities. The HESI ACSA tiered testing and evaluation approach "emphasizes toxicological endpoints and exposure durations that are relevant for risk assessment, provides greater efficiency, uses fewer animals, uses resources more wisely, and includes improved data for risk assessment purposes.[3]"

Currently, there appears to be considerable Federal resources devoted to basic research for development of new and novel test methods. By comparison, very little Federal resources appear to be devoted to translating these methods from the investigation phase to standardization of test protocols, and formal validation. Formal validation is a necessary step that must be achieved for a test method to be adopted and used in a regulatory program.[4] Because the current Federal funding approach seems to be primarily focused on basic research, new, revised and alternative methods will continue to have a very difficult time making it from the researcher's bench into a regulatory testing regimen. However, even if funding were made available for pre-validation and validation studies, without a strategic plan in place NICEATM and ICCVAM agencies would not have a clear path forward to devote such resources to the highest-priority activities. As it stands right now, the activities of NICEATM/ICCVAM appear to be governed more by a 'first come – first served' process than by a process designed to achieve the most impactful results on the highest priority issues that resources permit. Therefore, the 5-Year Planning process promises to provide a clear "road map" for NICEATM/ICCVAM to identify the highest priority objectives, to plan to achieve these objectives and to make real and lasting impacts across the Federal government on the development, validation and adoption of new, revised and alternative assays.

The charge to NICEATM/ICCVAM to develop a 5 -Year Plan is indicative of the challenges faced in developing, validating and adopting new and revised testing assays within regulatory programs. The process NICEATM/ICCVAM adopts to develop the 5-Year Plan must include means to address both (1) research, development, translation, and validation of new and revised assays for integration of relevant and reliable methods into federal agency testing programs and (2) identification of areas of high priority for new, revised or alternative assays for the replacement, reduction, and refinement of animal tests. We are pleased to see that there is recognition for broad stakeholder input into this process. However, collecting information via written comments just once in this process will be insufficient. We believe it is important to develop the 5-Year Plan over the course of the next several months in an open manner, and we suggest NICEATM/ICCVAM consider following the approach used by NTP in developing their Roadmap, which was structured around a series of stakeholder meetings/workshops. We believe that the process employed by NTP in developing the NTP Roadmap provides a good model that NICEATM/ICCVAM should follow. With such a series of workshops, the process for developing the 5-Year Plan would be open and inclusive of all stakeholders

---

[3] http://www.hesiglobal.org/Committees/TechnicalCommittees/ACSA/

[4] ICCVAM Authorization Act of 2000 (http://iccvam.niehs.nih.gov/about/PL106545.pdf). Each Federal agency carrying out a program described in subsection (a) shall ensure that any new or revised acute or chronic toxicity test method, including animal test methods and alternatives, is determined to be valid for its proposed use prior to requiring, recommending, or encouraging the application of such test method.

Specifically, we suggest NICEATM/ICCVAM consider holding three public meetings or workshops. The first workshop would be for scoping and development of models to collect and report information to address the questions and issues necessary for developing a 5-Year Plan[5]. We also

suggest that the process decided on at the first workshop consider including development of schematics for specific test methods, similar to that presented at the November 30, 2006 Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) meeting by Dr. Stokes,[6] that once finalized, would provide a useful summary of near-term and long-term objectives and on-going, planned or yet to be addressed, prevalidation and validation research. The outcome of the first workshop would be the approach that each ICCVAM agency would use to gather, organize and present the information needed to develop the 5-Year Plan. The second workshop would be designed for presentations by the ICCVAM agencies on their progress in applying the model for collecting and reporting information. The third workshop would be for presentation and discussion of the draft final report. With focus, such a series of workshops could be completed by late summer 2007.

The Council has repeatedly urged NTP to make better use of ICCVAM to review and evaluate alternative methods. The ICCVAM Authorization Act of 2000 (42 U.S.C. 2851) operates to ensure that any new or revised acute or chronic toxicity test method, including animal test methods and alternatives, is determined to be valid for proposed use prior to an Agency requiring, recommending, or encouraging the application of such test method. In moving forward with development of the 5-Year Plan, we believe it is particularly important to use an approach that will clearly present information in such a way that priorities can be set. Furthermore, the trajectories of each method identified as a priority must fully integrate method validation work into the path forward. Full embracement of validation studies is necessary, because these validation studies provide the critical scientific data and information needed to understand the relevance, reliability, and appropriate use of such methods. Inclusion of validation studies is necessary to assure consistency with the ICCVAM Authorization Act of 2000.

The Council appreciates this opportunity to provide early input on matters related to the development of the NICEATM/ICCVAM 5-Year Plan. Please don't hesitate to contact me via e-mail (Rick_Becker@americanchemistry.com) or by phone at (703-741-5210) if you have questions on ACC's comments and recommendations.

Sincerely,

*Original Signed By*

Richard A. Becker, Ph.D., DABT

---

[5] One model that may be discussed would encompass having each ICCVAM organization describe: What are the regulatory testing programs that each ICCVAM organization currently uses which employ in vivo testing? What are the objectives of each battery with respect to the use of the data? What are the objectives of each test method within the battery with respect to the use of the data? For each regulatory testing program, the model approach would direct appropriate Agencies to develop information along the lines of: What are options for refinement? For reduction? For replacement? Near term & long term? What research efforts are already underway? What's needed? What translational efforts are already under way? What's needed? What prevalidation work is already underway? What's needed? What validation work is already underway? What's needed?

[6] Slide 13 http://ntp-server.niehs.nih.gov/index.cfm?objectid=58A82A0C-F1F6-975E-72FAE774714C1F98