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Dear Dr. Birnbaum:

Thank you for meeting with us on April 13. We are writing to follow up on some of the items we discussed and, as you requested, to provide specific suggestions to improve ICCVAM's effectiveness and NIEHS' role in achieving the NRC vision for "Toxicity Testing in the 21<sup>st</sup> Century." As you are well aware of the history and background surrounding these issues, what we offering below is a concise list of specific suggestions.

### ***I. Reform of NICEATM/ICCVAM***

In order to achieve any effective toxicity testing program, ongoing translation of current biological technological discoveries into toxicological test methods is essential. ICCVAM was originally created to fill part of this need – the validation of new methods for toxicity testing, with an emphasis on the "3Rs" (refining, reducing and replacing the use of animals). However, it has become increasingly apparent that ICCVAM is not capable of performing this critical task, as we and others have documented in numerous examples (for extensive examples, please see our previous letter to you, sent February 10, 2009, our report documenting the differences between Europe and the U.S. in this regard, and our comments provided to NICEATM/ICCVAM regarding their 5-year plan on December 22, 2006 and June 7, 2007, all attached).

For examples of ICCVAM's slow progress, consider the case of cytotoxicity methods for the assessment of acute toxicity. ICCVAM first considered these methods in 2000. Following a workshop, ICCVAM published a report suggesting follow-up: "Continued development and optimization of such systems (as gut absorption, BBB passage, key kinetic parameters, and metabolism) for this application should be encouraged and should receive regulatory support" as well as concluding "...if the commitment to conducting a formal validation study was strong enough, the scientific resources could be harnessed for this effort with facility and the *in vitro* tests studied proved good enough, a replacement test battery might be achieved in as short a time as 2-3 years."<sup>1</sup> To the best of our knowledge, none of the suggestions have been taken up. In 2008, ICCVAM finally issued recommendations to agencies that cytotoxicity methods could be used to *set starting doses* for acute

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<sup>1</sup> National Institutes of Health. 2001. Report of the International Workshop on *In Vitro* Methods for Assessing Acute Systemic Toxicity. NIH Publication No: 01-4499  
([http://iccvam.niehs.nih.gov/docs/acutetox\\_docs/finalrpt/finalall0801.pdf](http://iccvam.niehs.nih.gov/docs/acutetox_docs/finalrpt/finalall0801.pdf))

toxicity testing. In the intervening seven years, ICCVAM has made no progress toward replacing the use of animals in acute toxicity testing.

Another example is that of Alternative Methods to Replace the Mouse LD50 Assay for Botulinum Toxin Potency Testing, which the Humane Society of the United States nominated in 2005, and which should have been a straightforward project. ICCVAM held a workshop to review the science and make recommendations; nothing further on this project has been done since, even though a non-animal method has been included in the European Pharmacopoeia for use in final lot product testing in Europe since 2005.<sup>2</sup>

A quite recent example of ICCVAM's ineffective process is that of the Independent Scientific Peer Review Panel Meeting: Evaluation of the Validation Status of Alternative Ocular Safety Testing Methods and Strategies, which was held May 19- 21, 2009. This peer review was ostensibly in response to the submission of an approach to assess ocular irritation by a consortium of manufacturers of antimicrobial cleaning products (AMCP) and the Institute for In Vitro Sciences (IIVS). The consortium had been working for several years to develop and evaluate a completely non-animal method to assign ocular hazard categories required for EPA registration of AMCPs and the consortium kept ICCVAM apprised of its activities from very early in the process (Len Sauers, Proctor & Gamble, personal communication). ICCVAM had been asked by EPA and the consortium to assess the general question of whether the proposed testing strategy would "assure EPA, with a reasonable degree certainty, that the Agency can make labeling decisions for antimicrobial cleaning products that appropriately inform the user?" ICCVAM had agreed to an expedited review; the extensive peer review therefore came as a surprise to the consortium. ICCVAM did not contact any of the participants in the consortium's effort to present the logic behind the proposal to the Peer Review Panel. When ICCVAM belatedly requested that IIVS present a description of the protocols, it expressly prohibited any discussion of data interpretation with panel members. As part of the review, ICCVAM took it upon itself to review the validation status of the "low volume eye test" (LVET) method, which is a refinement of the Draize rabbit test and is a method that provided some of the data for the consortium's validation studies. This additional review was unexplained since the European Centre for Validation of Alternative Methods (ECVAM) is currently reviewing this method and has in its possession a comprehensive Background Review Document for this purpose, yet ICCVAM decided to perform this duplicative review, having available only a subset of the data available to ECVAM. Since the Draize test is known to significantly over predict the human response, the LVET method was specifically designed to be less sensitive than the traditional Draize test and more predictive of humans. However, the ICCVAM peer review panel concluded that it was necessary to change the scoring system of the LVET to replicate exactly the Draize results. The Panel recommended a full validation study be done using approximately 50 chemicals to compare the LVET with the traditional Draize, even though ECVAM is currently reviewing this subject, and enough data already exists to compare the two methods. In addition, the Consortium provided both animal and *in vitro* data on more than 60 antimicrobial (or similar) cleaning products (which represent the major proportion of all AMCPs on the market) yet the Panel concluded that there were not enough data to make a determination.

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<sup>2</sup> European Pharmacopoeia. 2005: Ph Eur monograph (01/2005:2113).

It was evident from the Peer Review Panel discussion that the panel did not have a comprehensive view of the subject it was reviewing and apparently misunderstood its charge<sup>3</sup>. The stakeholders that were present, including representatives from participants in the consortium, were only allowed to comment *after* the panel had finished its discussion and made its recommendations. The Panel itself was not instructed that it could ask questions of the consortium members; therefore any real debate or discussion was prohibited between consortium members and the Panel.

In the meantime, due to the lack of progress of ICCVAM on this topic, the EPA has independently initiated a pilot program which will allow, under certain conditions, for the proposed non-animal testing strategy to be used to register AMCP with the EPA.

Validation of new and evolving technologies is becoming increasingly essential for realization of the NRC vision for toxicity testing in the 21<sup>st</sup> century. As it currently exists, ICCVAM is not able to keep up with validating existing traditional *in vitro* methods, let alone the hundreds of high-throughput, genomic, proteomic and systems biology approaches being developed. In fact, members of ICCVAM are strikingly and inexplicably absent from symposia and workshops discussing these new technologies, even though some of this development is actually occurring within the NTP. At the recent NAS Symposium on Risk Assessment, not only was no one from ICCVAM present, in his presentation, the Director of NTP, John Bucher included a slide entitled “Validation” that was otherwise blank, and offered no further enlightenment on the issue. While the way forward for determining the scientific adequacy of new high-throughput methods is yet to be developed, it is disheartening to say the least to see such a lack of leadership from the only official validation authority in the U.S. If the NRC vision is to be realized, the US desperately needs an entity capable of evaluating the new methodology for regulatory acceptance.

While some of the issues that have resulted in this slow progress are due to a lack of initiative and any sense of urgency from the members of ICCVAM, some are inherent in the structure and nature of the Committee itself. We distinguish two main categories of suggested improvements: those that have to do with the structure of ICCVAM and those that are more policy-focused.

### ***A. Structure***

As a stand-alone, “coordinating” committee, ICCVAM is limited in its ability to proactively identify methods that are ripe for validation, to perform any validation studies of its own, or to mandate use by the relevant Agencies of any methods that it deems validated. In effect, ICCVAM’s infrastructure is inadequate with respect to its ability to carry out its mandate.<sup>4</sup>

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<sup>3</sup> This is a continual concern within the ICCVAM process, and it has been raised by us on at least two other occasions, most notably with regard to the ICCVAM review of five *in vitro* pyrogenicity methods in February 2007. See comments attached.

<sup>4</sup> Which, according to the ICCVAM Authorization Act, Public Law 106-545, is to:

- (1) increase the efficiency and effectiveness of Federal agency test method review;
- (2) eliminate unnecessary duplicative efforts and share experiences between Federal regulatory agencies;
- (3) optimize utilization of scientific expertise outside the Federal Government;
- (4) ensure that new and revised test methods are validated to meet the needs of Federal agencies; and
- (5) reduce, refine, or replace the use of animals in testing, where feasible.

Rather, ICCVAM is a passive participant: it reacts to nominations from third parties and is then unable to follow-through on its own recommendations. For example, following a test method review, ICCVAM often makes recommendations for further validation studies to increase the potential for a successful second review. However, ICCVAM cannot perform this research or even request that the research be done by some other entity.

This situation contrasts dramatically with that of the European Center for the Validation of Alternative Methods (ECVAM) which was established in 1992 as a unit of the Environment Institute, part of the Joint Research Centre (JRC). ECVAM is a division of the EC's JRC Institute for Health and Consumer Protection (IHCP) and is housed in IHCP facilities in Ispra, Italy. It receives approximately 25 million € per year from the E.U. Directorate General on Research and has approximately 60 staff members, roughly half of whom work directly in laboratories. ECVAM can proactively identify priority work areas and develop and validate methods on its own or in collaboration with others. ECVAM has established working groups in 15 key areas, including: systemic toxicity, topical toxicity, sensitization, carcinogenicity, reproductive toxicity, ecotoxicity, biologicals, nanotoxicology, and computational toxicology, and maintains a comprehensive database on alternative methods, including those validated by ECVAM.

According to Public Law 106-545, ICCVAM is comprised of the representatives from each of the 15 agencies that “develops or employs tests or test data using animals, or regulates on the basis of the use of animals in toxicity testing”. The methods reviewed by ICCVAM are not relevant to most of these Agencies, yet any member of ICCVAM can participate in method review, regardless of their expertise or lack thereof, which suggests that the composition of ICCVAM should be revisited. Members of ICCVAM should be restricted to those Agencies with vested interest in methods under review.

The law also states that ICCVAM members shall be the heads of member agencies or their designees, yet the members of ICCVAM are generally not those who have authority within their respective agencies to ensure the use of ICCVAM-recommended methods. In addition, ICCVAM positions are voluntary; in most cases ICCVAM members have other, full-time agency responsibilities and ICCVAM activities are not a priority.

Finally, the current Executive Director of ICCVAM is also the Director of ICCVAM's administrative organization, the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), and is also the NIEHS representative on ICCVAM. This triple assignment represents a conflict of interest on multiple levels (not the least of which is that the ED of ICCVAM should not have the prerogative of choosing members of its advisory committee, Scientific Advisory Committee on Alternative Toxicological Methods (SACATM)). Each of these three positions should be independent.

We are also concerned that the process of choosing members of SACATM is not transparent, nor is it apparent who is accountable for appointing members. Like members of ICCVAM itself, members of SACATM should be chosen based on their expertise in the area of non-animal test method development and/or the application of the 3Rs to testing policy. For the last several nomination rounds, the U.S. animal protection community has nominated several individuals with significant experience in both non-animal method development and policy, yet, since the nomination of Dr.

Martin Stephens (Humane Society of the United States), the “animal welfare” representative has not been chosen from among these qualified nominees. The selection of SACATM members based on personal interactions, relationships, or preference should be expressly prohibited.

In light of the above and to improve ICCVAM’s performance we suggest the following:

- ICCVAM should be able to proactively identify methods for development
- ICCVAM should have access to the infrastructure required to follow-up on test method development or validation. If it is not possible to create infrastructure for ICCVAM, including lab space and staff, within the NIEHS, ICCVAM should be able to request studies from other NIEHS departments or governmental organizations (e.g. EPA).
- The Executive Director of ICCVAM and Director of NICETAM should be separate positions, ***held by individuals with demonstrated commitment to the advancement of non-animal methods.***
- The NIEHS representative on ICCVAM should not be either the Director of ICCVAM or the Director of NICETAM.
- Agencies involved in assessing methods via ICCVAM should be limited to the Agencies to which the method is relevant, and may include more than one representative from each agency on an ad-hoc basis.
- ICCVAM membership should include a paid full-time position and agency representatives should have the ability to ensure implementation of ICCVAM-recommended methods within their agency. Each agency may provide additional representatives as needed, based on expertise relative to a given project, on an ad-hoc basis.
- Members of SACATM should be chosen by a transparent process.
- Agency representatives to ICCVAM should be chosen using the following criteria:
  - commitment to reducing the use of animals in testing
  - knowledge of *in vitro* test method development and the use of such data in risk assessment

## ***B. Policy***

*Relate alternative method development to regulatory needs and coordinate ICCVAM and Agency activities*

Although ICCVAM’s activities are presumably in support of member Agencies’ needs, there is a disconnect between ICCVAM’s activities and the policies and activities of member Agencies. A suggestion for rectifying this is to have member agencies provide ICCVAM with a description of regulatory testing programs involving the use of *in vivo* tests and how the data are used in risk assessment. ICCVAM should also compile a list of translational activities currently underway within each agency and within other parts of NIH/NIEHS. In this way, ICCVAM could identify areas of need as well as barriers to the use of non-traditional methods and plan short and long-term goals accordingly. These activities could be the responsibility of each Agency representative to ICCVAM (which would be facilitated if Agency representatives were full time staff). This type of analysis was what we were hoping to see during the process of creating the congressionally-mandated Five Year Plan, completed by ICCVAM in 2008.

*Prioritization based on 1) readiness, 2) numbers of animals involved, and 3) replacement*

Readiness includes short-term achievability (e.g. skin and eye irritation, non-animal skin sensitization, endocrine mechanistic assays), methods in progress by Agencies or other departments [high-throughput screens, quantitative structure-activity relationship modeling (QSAR)], or immediate need. Prioritization by numbers of animals would include carcinogenicity and reproductive and developmental toxicity. Finally, of the “3Rs,” replacement can and should be considered the primary objective.

ICCVAM should also take into account international activities, such as those of the European Partnership for Alternative Approaches to Animal Testing (EPAA; <http://www.epaa.eu.com>), which recently surveyed its more than two dozen corporate partners to identify 3Rs methods used in-house that could potentially be brought into the mainstream. The EPAA reports that as of November 12, 2006, 114 candidate 3Rs methods have been identified, of which:

- 56 percent were geared at replacement; 31 percent reduction; 13 percent refinement.
- 57 percent were applicable to the chemicals sector; 35 percent pharmaceuticals; 17 percent animal health; and 5 percent agrochemicals (Webb, 2006).

*Integration of ICCVAM priority efforts with other agencies, industry and academia.*

Again, a model for this kind of activity exists in Europe; European government institutions and corporate partners are currently providing more than €80 million in funding under for 13 targeted, multi-year 3Rs research projects (Hartung, 2006), including the following:

- *ReProTect* (<http://www.reprotect.eu>): An EU integrated project budgeted at €13.9 million (EC contribution €9.1 million) aimed at developing the concepts required to develop 3Rs testing strategies in the areas of reproductive and developmental toxicity.
- *ACuteTox* (<http://www.acutetox.org>): An integrated project budgeted at €15.7 million (EC contribution €9 million) aimed at optimizing and pre-validating an *in vitro* testing strategy for predicting acute toxicity in humans.
- *Sens-it-iv* (<http://www.sens-it-iv.eu>): A multi-stakeholder integrated project to develop novel testing strategies for *in vitro* assessment of allergens.
- *PredictOmics*: An integrated project budgeted at €3.4 million (EC contribution €2.3 million) aimed at developing short-term *in vitro* assays to evaluate long-term toxicity.
- *BioSim* (<http://www.biosim-network.net>): An EU Network of Excellence comprised of 26 academic, 10 industrial and 4 regulatory partners mandated to develop *in silico* simulation models of cellular, physiological and pharmacological processes to provide a deeper understanding of biological processes.
- *OSIRIS (Optimized Strategies for Risk Assessment of Industrial Chemicals through the Integration of Non-test and Test Information)*: Integrated project with an EC contribution of

€10 million and estimated 4.5 year duration, which addresses the reduction of animal tests in the implementation of the REACH regulation through the application of “Intelligent Testing Strategies.”

There are several initiatives in the U.S. with which ICCVAM could be involved and form an integrating partnership. The Tox21 project is an obvious partner as much of the activity is housed within NIEHS, yet ICCVAM is ill-prepared for evaluating the regulatory translation of these high-throughput in vitro methods. Similarly, there is much activity within the FDA and industrial partners developing QSAR and other computer-assisted tools for risk assessment of multiple human health-related endpoints ([http://www.leadscope.com/fda\\_model\\_appliers](http://www.leadscope.com/fda_model_appliers), and <http://www.leadscope.com/news>). In addition, The Hamner Institute (<http://www.thehamner.org>) has become a forerunner in elucidating biological pathways and developing databases applicable to predicative toxicology.

However, before ICCVAM can effectively initiate further collaborations, the structural changes suggested above would need to be implemented (to alleviate problems as described above during ICCVAM’s involvement in the antimicrobial cleaning product manufacturer consortium’s effort to validate a method for eye irritation labeling).

*Non-duplicative, expedited process for methods developed/ reviewed in other countries*

For specific suggestions in this regard, see the attached comments on ICCVAM’s 5-year plan. The recent announcement of the creation of ICATM is a step in this direction; however, if past performance is predictive of future activity, the value of ICCVAM’s participation will be mitigated by its slow process and reluctance to embrace new approaches. For example, in 2007, a leaked email from the Chair of ICCVAM (written at the request of the Executive Director) expressed “concern” regarding the concept of evidence-based toxicology [promulgated by Dr. Thomas Hartung], especially the notion that “we are validating in vitro assays against the wrong standard when we use animals because animal studies don’t do a good job of predicting human responses” and that “they” are “trying to build a case to not use animals for any testing.”<sup>5</sup> The email was sent to a number of government officials as well as outside contacts with the request for responses that would “help us try to combat these papers.” Dr. Hartung was then head of ECVAM and is now the head of the Center for Alternatives to Animal Testing (CAAT) at Johns Hopkins, where he occupies an endowed Chair for the Study of Evidence-based Toxicology. What is truly shocking is the reaction of ICCVAM (the only group in the US charged with the validation of alternative methods) to a new idea that could reduce the reliance on animals in safety testing.

Given all these facts, one can reasonably conclude that, without significant revision in accordance with the recommendations above, it is likely that ICCVAM will continue to be a hindrance, rather than an asset, to the development and use of non-animal methods, both in the U.S. and internationally.

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<sup>5</sup> Copy of the e-mail attached.

### *Transparent advisory and peer review panel selection processes*

The nomination of members to ICCVAM's Scientific Advisory Panel for Alternative Toxicological Methods (SACATM) has been a confusing and secretive process. Nominations for the 2009 term were not selected and selections for the 2010 term have not yet been announced, despite continuing and growing vacancies, and the announcement of an upcoming meeting. The Charter creating SACATM ([http://ntp.niehs.nih.gov/files/Charter\\_1-14-08\\_508.pdf](http://ntp.niehs.nih.gov/files/Charter_1-14-08_508.pdf)) suggests that SACATM meet "up to twice a year". Historically, SACATM has met once a year; in order to build momentum behind ICCVAM's activities, SACATM should meet twice a year.

ICCVAM's method peer review panels are often comprised of members with admirable depth and breadth of knowledge of the academic fields related to the methods being considered. However, this academic rigor is often attained at the expense of practical knowledge of the purpose or use of the methods being reviewed or the validation process itself, and members often do not have experience with the challenges that are faced during the conduct and interpretation of validation studies. Too often, to quote Voltaire, "The perfect is the enemy of the good." When choosing peer review panel experts and briefing experts on the methods to be reviewed, ICCVAM and NICEATM must consider these concepts to ensure efficient and meaningful method reviews.

### ***II. Role of NIEHS in Implementation of the National Research Council's Vision for Toxicity Testing in the 21<sup>st</sup> Century: Beyond the MOU***

The announcement last year of a "Memorandum of Understanding between NIH, HHS and EPA High Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings" is a positive step toward achieving the vision for toxicity testing outlined in the NRC report, *A Vision for Toxicity Testing in the Twenty-first Century*, published in 2007. This collaboration will greatly facilitate the development and interpretation of high-throughput methods; however, a much more comprehensive approach is required to achieve the NRC's vision, and there are ample opportunities for an expanded role of NIEHS.

NIEHS could stimulate basic and translational research through a combination of basic research and special initiative grants. For example, particularly applicable would be basic research grants targeting the areas of identification of biological pathways of toxicity, toxicity-related biomarkers, molecular and genetic epidemiology, virtual tissues, relating molecular perturbations to toxic effects. Special initiatives focusing on the areas of translational research, incorporation of metabolism into *in vitro* methods, and validation of methods would greatly improve the acceptance and use of the developing technology. We were encouraged to learn of promising steps in this direction, namely five new categories of SBIR grant initiatives to be introduced this fall which we understand to include the subjects of HTS screens for metabolism and bioinformatics tools.

NIEHS could also be a leader in the implementation of new technology: as new tools become available NIEHS could apply these tools into the NTP nominations process. In current practice, NTP usually recommends new testing for the chemicals it evaluates, even though in most cases the chemicals have already been studied extensively. Even when toxicity data for humans exists or is readily obtainable, as in the case of FDA-approved drugs like hydroxyurea and fluoxetine (Prozac), NTP recommends additional testing on animals. NTP continually solicits nominations of chemicals to

be evaluated from the general public as well as the scientific community (for example, Prozac was nominated for evaluation by a single anonymous individual who did not even provide a reason for the nomination; it would seem to be in the interest of fair and open government procedures that chemical nominations be the subject of greater scrutiny). The NTP process could benefit from the incorporation of new assessment tools; for example, experts in computational toxicology and integrated testing strategies could be included in expert panels reviewing study nominations, and the new technology and strategies developed through Tox21 could be incorporated into NTP study plans. To ensure accountability as these new approaches are integrated, and to provide feedback for stakeholders who intend to comment regularly on test nominations, NTP should consider adopting a “response to comments” document or other transparent mechanism that details how or when alternative information or tests were considered and were or were not used, and why. This would provide a more continuous picture of the NTP chemicals nomination process, from agent nomination through test completion.

In conclusion, NIEHS is uniquely positioned to play a central role in achieving the vision for toxicity testing in the 21<sup>st</sup> century, as laid out by the NRC. Through restructuring of ICCVAM, focused funding of related research and translation, and implementation of the new technologies within its own programs, NIEHS could be instrumental in seeing the NRC vision become a reality.

We appreciate your consideration of these suggestions, and look forward to constructive dialogue with your office.

Sincerely,

(signature redacted)

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