PCRM PHYSICIANS COMMITTEE FOR RESPONSIBLE MEDICINE

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These comments on the draft NICEATM-ICCVAM Five-Year Plan (2013-2017) are submitted on behalf of People for the Ethical Treatment of Animals (PETA) and the Physicians Committee for Responsible Medicine (PCRM). Our organizations are committed to using the best available science to save animals from suffering in toxicity testing and promote the acceptance of human-relevant methods for risk assessment.

This plan, once again, receives a failing grade because it:

1. inappropriately repeats or retains many of the priorities of the last five-year plan (2008-2012), showing both a lack of progress and an inability on ICCVAM's part to move forward;

2. demonstrates a lack of knowledge of—or perhaps unwillingness to acknowledge—some of the key advances in regulatory testing and validation theory that have taken place over the past couple of years;

3. clearly prioritizes refinement over replacement and reduction measures;

4. includes statements that undercut the few *in vitro* methods or approaches ICCVAM has recommended, and

5. lacks key details that would allow NICEATM-ICCVAM and stakeholders to track progress and success, especially of NICEATM-ICCVAM's goals to "Promote the Application and Translation of Innovative Science and Technology" and "Facilitate Regulatory Acceptance and Use of Alternative Methods."

GENERAL COMMENTS:

The document often uses words like "promote, foster, advance, facilitate, and strengthen" to describe the actions NICEATM-ICCVAM plans to take in the next five years. Unfortunately for stakeholders, words like these provide no solid basis for measuring progress. What metric does one use, for example, to quantify "fostering?" With the

exception, perhaps, of sponsoring one or two workshops between now and 2017, there are few concrete goals described in the plan and no timeframes set for achieving progress. NICEATM-ICCVAM should be playing a leadership role in bringing about change and achieving the 21st Century Toxicity Testing vision; instead, the plan relegates the entities to a peripheral, supportive role at best, and to an obstacle at worst.

Strategic Opportunity 1: Promote the Application and Translation of Innovative Science and Technology

While this section provides an impressive list of activities being undertaken at ICCVAM member agencies, the section lacks specific details on what NICEATM-ICCVAM will do to "facilitate," "promote," or "foster the adoption of" new methods in these areas. It even lacks details on the manner in which these new technologies will serve to replace or reduce animal tests (e.g., stem cells, three-dimensional cell cultures, and biological networks). While a list of partner agency activities is interesting, effective planning on NICEATM-ICCVAM's part requires specific details regarding the manner in which these technologies can further the replacement or reduction of animal tests, and what NICEATM-ICCVAM will do to foster their development or implementation.

With regard to "Integrated Testing and Decision Strategies," we are pleased to (finally) see acknowledgement of the usefulness of testing strategies to regulatory assessment. However, it should be noted that there is a long history of the use of this concept in the US and abroad, entitled Integrated Approaches to Testing and Assessment (IATA)", which began with an EPA-hosted OECD workshop in 2007.[1] EPA, OECD, and others have done quite a bit to build upon the IATA concept since that workshop, including the creation of the Adverse Outcome Pathway (AOP) approach, which this plan refers to as an "ITDS approach" used by the Chemical Safety for Sustainability Research Program. An AOP links adverse effects to perturbations in specific toxicity pathways, and can be used to both describe the available evidence linking a substance or mechanism of action to an apical adverse effect and identify test methods that are available or need to be developed to query key events along the pathway.

The AOP approach is a natural extension of the "toxicity pathways" concept described by the National Academy of Science in its 2007 report *Toxicity testing in the 21st Century: A vision and strategy*[2], a natural maturation of the IATA concept, and is critical to accomplishing the vision that was set out by the National Academies in 2007, as well as the remit of NICEATM-ICCVAM. It is alarming that AOPs are not even mentioned in this plan particularly given the history detailed above and the fact that the EPA CSS

[1] OECD (2008) Series on Testing and Assessment No. 88: Workshop on Integrated Approaches to Testing and Assessment. Available at: http://www.oecd.org/chemicalsafety/testingofchemicals/40705314.pdf. Accessed August 9, 2012.

[2] The National Academies. (2007) *Toxicity testing in the 21st Century: A vision and strategy.* National Academies Press. Washington, DC. Available at http://www.nap.edu/catalog.php?record_id=11970. Accessed August 9, 2012.

Research Program's recently-released *Strategic Research Action Plan: 2012-2016*[3] uses AOPs as a guiding concept and foundation for its strategic planning.

We are pleased to see that ICCVAM supports many of the areas being focused on by EPA's Chemical Safety for Sustainability (CSS) research program, such as systems biology approaches, high throughput screening, computational predictive models, development of biomarkers, and integrated testing strategies. In order to take full advantage of these rapidly evolving tools, however, it is imperative that appropriate methods of validation, which are more streamlined and less focused on lengthy cross-laboratory testing, be developed and agreed upon by regulatory entities. Current processes used for validating test methods proposed for regulatory testing guidelines simply do not allow this to occur in a timely manner. A prime example of this is the fact that it took ICCVAM more than seven years to validate the Bg1Luc (Lumi-cell) assay for ER transactivation.

Validation of alternative methods has been a topic of discussion in the literature lately[4,5] and it is clear that a different approach is needed. Arguments have been made for the use of performance standards and EPA research and program staff, in collaboration with NIH, the European Centre for the Validation of Alternative Methods (ECVAM), industry and academia, present issues and possible solutions with regards to validation of HTP assays supporting the 21st century toxicity testing vision[6]. To date, ICCVAM has shown little innovation in and made few contributions to developing 21st century toxicology validation methods.

Strategic Opportunity 2: Advance Alternative Test Methods and Testing Strategies

ICCVAM notes that the first 2008-2012 NICEATM-ICCVAM Five-Year Plan described the specific priority areas for new alternative test methods and that it will continue to actively pursue improvements in test methods in these established priorities. The very fact that these priority areas remain the same demonstrates a lack of overall progress.

In the introduction to this section, the plan mentions the need to consider "available human, animal, and environmental reference data from ethical and intentional and accidental exposures…" during evaluation of new test methods. This is not news! The difficulty of validating new tests by comparing them to the old animal tests is well established and has been a known barrier for more than a decade. This plan should have described specific actions NICEATM-ICCVAM has undertaken or plans to undertake to address this well-known problem.

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[3] US EPA. (2012) *Chemical Safety for Sustainability Strategic Research Action Plan: 2012-2016.* EPA 601/R-12/006. Available at: http://epa.gov/research/docs/css-strap.pdf. Accessed August 9, 2012.
[4] Hartung, T. (2007). "Food for thought ... on validation." ALTEX 24(2): 67-80.
[5] Leist, M., et al. (2010). "Food for thought ... considerations and guidelines for basic test method descriptions in toxicology." ALTEX 27(4): 309-317.
[6] Judson R. et al. (2012) Perspectives on validation of high-throughput pathway-based assays supporting the 21st century toxicity testing vision. Presented Evidence Based Toxicology Workshop, RTP NC 1/2012.

Testing of Vaccines and Other Biologics

ICCVAM's lack of progress in the area of biologics and vaccines testing is exceptionally troubling when one considers the tens of millions of animals who suffer and die each year to verify vaccine potency and safety. The European Pharmacopoeia lists nine methods that reduce animal testing and one *in vitro* method that replaces animals in testing the potency of human vaccines; of these, two have been validated and endorsed by ECVAM. In stark contrast, ICCVAM has reviewed and recommended one alternative testing method as a *refinement* of the rabies vaccine potency test. There has been little effort by ICCVAM to reduce or replace animal testing for vaccine potency or safety, and NGOs have had to step into the vacuum created by ICCVAM.[7]

With regard to *Leptospira interrogans* and *Leptospira kirschneri* vaccines, USDA Supplemental Assay Methods (SAM) 624, 625, 626, and 627—all of which have been approved for use since 2009—allow for the use of the sandwich ELISA method for serovars pomona, canicola, icterohaemorragiae, and grippotyphosa. The successful implementation of these analytical methods (in lieu of the hamster test) has been approved and adopted by USDA as well as the pharmaceutical industry. Since the USDA is the agency that oversees the use of *Leptospira* vaccine potency testing and it has announced that this project is completed with respect to method validation, ICCVAM should not be involved in this one-agency issue.

With the ever-mounting demand for botulinum toxin potency testing for cosmetic, food, and wildlife monitoring , the number of animals killed in order to determine the LD50 of each batch of toxin also continually increases. PETA submitted comments[8] related to the botulinum toxicity testing suite that BioSentinel, Inc. developed and submitted for validation by ICCVAM. We recommend using a combination of existing validation data from BioSentinel and the collaborating pharmaceuticals so that a sensitive, *in vitro* assay could replace the LD50 assay currently in use. For some time, the SNAP25 Endopeptidase Assay has been listed by European Pharmacopoeia (Ph. Eur.) as a replacement to the mouse LD50 assay for botulinum toxin potency testing, yet ICCVAM neglected to recommend this replacement test as well.[9]

The plan notes that "In the next five years, NICEATM and ICCVAM will evaluate alternative test methods and testing strategies for testing BoNT and will facilitate the acceptance of appropriate test methods and humane endpoints. One priority will be an international workshop to review the currently available alternative methods for BoNT detection and quantification." Considering the large number of animals used and the significant unrelieved pain and stress they experience, this workshop should be given the highest priority and take place within the coming year. However, as you are aware, ICCVAM held a similar workshop in 2006 (Scientific Workshop on Alternative Methods to Refine, Reduce, and Replace the Mouse LD_{50} Assay for Botulinum Toxin Testing);

[7] Dozier, S. et al. (2011) Bridging the Gap Between Validation and Implementation of Non-Animal Veterinary Vaccine Potency Testing Methods. *Animals*, 1:414-432

[8] June 9, 2011 letter to Dr. Lori White.

[9] European Pharmacopoeia, 5th Edition, 2005.

one of the stated objectives of that workshop was to "To review the state-of-the-science and current knowledge of alternatives that may reduce, replace, and refine (less pain and distress) the use of mice for botulinum toxin testing." We recommend that NICEATM-ICCVAM and its SACATM carefully review and state in advance discrete goals against which performance and impact of this type of activity can be evaluated.

ICCVAM's stated goal of supporting the use of humane endpoints for all challenge tests has not resulted in the coordinated promotion of this position among U.S. agencies. USDA's strong suggestion that biologics licensees and permittees should modify eligible products' Outlines of Production to include descriptions of humane endpoints, for instance, has not been recommended for consideration by FDA for human vaccines involving similar challenge tests.

Acute Systemic Toxicity Testing

Although ICCVAM prepared a guidance document more than a decade ago describing how to use two *in vitro* test methods to estimate starting doses for acute oral systemic toxicity tests, evaluation of testing models which completely replace the need for *in vivo* animal testing has been glaringly absent.

The European ACuteTox project, the first attempt to create an integrated testing strategy based solely on *in vitro* and *in silico* methods, recently reported the results of its prevalidation of a tiered testing strategy using eight *in vitro* assays. The outcome of this study reinforced previous results obtained with the 3T3 NRU assay, supporting its use to identify unclassified substances (LD50 > 2000 mg/kg) as a first step in a tiered testing strategy. The project also identified of a number of *in vitro* assays that were able to flag substances as neurotoxicants and nephrotoxicants. These *in vitro* assays could be used to alert on tissue specific toxicity for substances that are identified as toxic with 3T3 cells. HepaRG™ cells (Life Technologies, Inc.) are an example of an alternative model for acute oral toxicity. HepaRG™ cells are capable of metabolizing compounds and remain sensitive to toxicity of metabolites. Rather than undertake a proactive review of this method as a replacement for animal testing, ICCVAM is admittedly allowing the burden to fall on ECVAM for validation and review of HepaRG™ cells.[10]

Importantly, the requirement to ascertain acute toxicity has been removed from the International Council on Harmonization (ICH) M3 guidelines for non-clinical safety studies for human clinical trials of pharmaceuticals.[11] The current revision of these guidelines states that when acute toxicity information is available from any study, separate single-dose studies are not recommended. With regard to whether acute toxicity

[10] Ibid

[11] ICH, 2009. Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals M3(R2). Available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2__Guideline.pdf

testing is still necessary to predict the consequences of human overdose, Chapman et al.[12] report a consensus among representatives from poison centers, the pharmaceutical and chemical industries, and regulatory bodies that the information it provides is of little value. This is partly because high doses of chemical substances often elicit non-specific effects in animals that have no relevance to incidences of human overdose. In addition, acute toxicity testing typically does not provide information on adverse and functional effects, target organ toxicity, and toxicokinetics that is considered by poison centers to be most useful.

The remaining driver for the conduct of acute toxicity studies is for the classification and labeling of chemicals.[13] However, the ACuteTox project analyzed the consistency in classification of the 97 chemical substances included in the project. The analysis showed that based on the ranges of their reported LD50 values, only approximately 50% of the substances fall unequivocally into a single class (with at least 90% probability). Approximately 40% fall within the limits of two adjacent classes and the remaining 10% fall into three or more different classes,[14] leading the authors to recommended revision of the GHS and CLP systems.

According to the plan, NICEATM-ICCVAM will focus on the dermal route of exposure for acute systemic testing. ICCVAM should not promote the "up-and-down" procedure which subjects animals to extreme pain and death. Instead, it should focus on the "evident toxicity" concept developed by UK scientists, which prevents administration of truly lethal concentrations by ending the test at the dose before that likely to be lethal, based on the evident toxicity of the animals.[15]

Promotion of the evident toxicity concept is the very least that can be done in this area. There is actually question as to whether the acute dermal systemic toxicity test be conducted at all, given that regulatory decisions could be made on oral acute data alone[16] or in combination with an assessment of the dermal penetration potential of a substance, which can be assessed using *in vitro* or *in silico* means.

Ocular Toxicity Testing

First, we feel obligated to point out that the use of frightening statistics to emphasize the need for careful validation of alternatives to replace the rabbit ocular toxicity test, in the context of this plan, is not only unwarranted but also illogical. The 125,000 eye injuries

[12] Chapman, K. et al. (2010) The Value of Acute Toxicity Studies to Support the Clinical Management of Overdose and Poisoning: A Cross-Discipline Consensus. *Regulatory Toxicology and Pharmacology*, 58:354–359.
[13] Seidle, T. et al. (2010). Cross-Sector Review of Drivers and Available 3Rs Approaches for Acute Systemic Toxicity Testing. *Toxicological Sciences*, 116(2): 382–396.
[14] AXLR8, 2011. Alternative Testing Strategies Progress Report 2011. Available at: http://axlr8.eu/assets/axlr8-progress-report-2011.pdf.
[15] van den Heuvel MJ, Clark DG, Fielder RJ, *et al.* (1990). "The international validation of a fixed-dose procedure as an alternative to the classical LD_{50} test". *Food Chem. Toxicol.* **28** (7): 469–82.
[16] Seidle T et al. (2011) ALTEX. Examining the regulatory value of multi-route mammalian acute systemic toxicity studies. 28(2):95-102.

estimated to be caused by "common household products such as oven cleaner and bleach" in 2012 occurred despite those products having all been tested on rabbits at some point in their development, and labeled as being dangerous to ocular health. These injuries have absolutely nothing to do with NICEATM-ICCVAM's remit to replace the rabbit test, and fear-mongering by ICCVAM is not appropriate.

In vitro test methods for the evaluation of eye irritants and corrosives include EpiOcular™ and SkinEthic Human Corneal Epithelial (HCE)™ which are based on 3-dimensional models using human corneal epithelial cells. Currently, more than 100 products have been tested and reported in the literature using the EpiOcular™ tissue model. Both EpiOcular™ and SkinEthic HCE™ methods are currently undergoing prevalidation by ECVAM for use in an assay for ocular irritation. The replacement of *in vivo* animal models with reconstructed human tissue offers the possibility of more efficient and relevant systems for the identification of eye irritants and corrosives.

ICCVAM failed to appropriately review an industry-initiated and sponsored program to use completely non-animal methods for assessing eye irritation for anti-microbial pesticides. In response to ICCVAM's rejection of this approach, the EPA issued its own pilot program accepting data thus generated.

Furthermore, this plan lists as a priority "…to implement procedures to avoid or minimize unrelieved pain and distress…" The replacement (not the refinement) of the use of rabbits in eye testing should have been ICCVAM's priority and since ICCVAM has already initiated an OECD project to include refinements into OECD TG 405, this refinement priority should be deleted.

Dermal Toxicity Testing

Progress has been made in the area of replacing animal models for acute skin toxicity testing. ICCVAM has recommended "four *in vitro* corrosivity test methods for use … in an integrated testing scheme for dermal corrosion and irritation."[17] These methods include Corrositex® (InVitro International), Rat Transcutaneous Electrical Resistance (TER) assay, EpiSkin™ and EpiDerm ™. ECVAM endorsed EpiSkin™ and EpiDerm™ as replacements for rabbit skin corrosivity tests in April and May 1998, respectively. However, ICCVAM has recommended that all samples which produce negative results in the *in vitro* corrosivity tests be tested *in vivo* for confirmation of results, refusing to take weight-of-evidence and other non-animal methodologies into account and increasing repetitive testing and animal suffering. Further, ECVAM did most of the work on the validation studies that quickly resulted in an Organization of Economic Cooperation and Development (OECD) test guideline,[18] with ICCVAM participating mostly in an advisory role. The validation materials listed on ICCVAM's website are all from ECVAM, with the exception of ICCVAM's comments. It is disturbing that this plan

[17] Biennial Progress Report 2008-2009, ICCVAM

[18] TG 439 (2010): *In Vitro* Skin Irritation: Reconstructed Human Epidermis Test Method. This TG covers the EPISKIN™-RHE (Skin Ethic), EpiDerm-SIT (MatTek) and SkinEthic RHE (Skin Ethic) methods.

simply fails to mention the available skin irritation test methods, which have been endorsed in the form of OECD Test Guideline 439 since 2010.

ICCVAM's recent review of the local lymph node assay (LLNA) did not include a review of substances that would allow its use by the FDA for pharmaceutical dermatologic formulations, and the FDA's response to ICCVAM's recommendations stated that the FDA "is eagerly anticipating a battery of *in vitro* tests to assess dermal sensitivity as a screen for human dermal sensitivity."[19] This response points to a lack of consideration of agency needs in ICCVAM's review of the LLNA.

This plan alludes to, but does not mention, an ongoing validation study of several *in vitro* methods for dermal sensitization determination.[20] In fact the OECD may soon begin work on test guidelines, following its adoption of an AOP for dermal sensitization.[21] While we of course do not suggest NICEATM-ICCVAM duplicate efforts by conducting its own validation study, what efforts will NICEATM-ICCVAM make over the next five years to ensure implementation within US regulatory programs?

Endocrine Disruptor Testing

More than a decade ago, during the planning stages of ICCVAM, the Endocrine Disruptor Screening Program (EDSP) was used as an example of a program that would benefit from the creation of ICCVAM, yet in the subsequent years, ICCVAM has barely made a contribution. Several of the methods were reviewed through the OECD, and the EPA carried out its own validation exercises for the remainder of the assays. ICCVAM has validated only one new assay, the BG1Luc ER TA assay, and that took seven years to complete, an excessive amount of time for a test that already had a considerable amount of relevant data associated with it. Based on a very high concordance of this assay with the ER rat cytosol binding assay, we urged ICCVAM to consider it as a replacement for the latter, which though billed as an *in vitro* test actually consumes large numbers of animals through harvesting of uterine tissues to collect cytosol. Similarly, a high concordance of this assay with the uterotrophic assay suggested it as a replacement for this *in vivo* test, particularly if *in vitro* metabolizing systems were added. Yet, there is little evidence that ICCVAM has pursued investigation of either of these two potential animal saving possibilities. The second validation ICCVAM has undertaken in this area, i.e., for the CertiChem Inc. MCF-7 Cell Proliferation Test Method, began in 2006 and six years later still has not been completed.

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[19] January 6, 2011 letter from Dr. Jesse Goodman, Food and Drug Administration, to Dr. William Stokes. Available at: http://iccvam.niehs.nih.gov/methods/immunotox/transmitJune10/FDA-Response.pdf.

[20] ECVAM Technical Report on the Status ofAlternative Methods for Cosmetics Testing(2008-2009). Available at: http://ec.europa.eu/consumers/sectors/cosmetics/files/pdf/animal_testing/at_ecvam_2008-2009_en.pdf.

[21] The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins Part 1: Scientific Evidence. Available at: http://search.oecd.org/officialdocuments/displaydocumentpdf/?cote=env/jm/mono(2012)10/part1&doclanguage=en.

Meanwhile, EPA recently released an overview of its Endocrine Disruptor Screening Program for the 21st Century (EDSP21) Work Plan, subtitled *The Incorporation of In Silico Models and In Vitro High Throughput Assays in the Endocrine Disruptor Screening Program (EDSP) for Prioritization and Screening*. In the short term, EDSP21 will use existing data, *in silico* models, and *in vitro* high throughput (HTP) assays to prioritize chemicals for Tier 1 screening, thereby reducing animal use. Its intermediate goal (2-5 years) is to use validated HTP assays and *in silico* methods to replace current validated *in vitro* assays and use the results to target *in vivo* assays, and reduce animal use accordingly. Its stated long-term goal is the full replacement of *in vivo* screening assays with validated *in vitro* HTP assays and *in silico* methods, eliminating the use of animals for screening purposes altogether. This again demonstrates the necessity for timely and appropriate validation procedures that keep up with changing science and meet agency needs, a requirement that ICCVAM's approach to validation is not capable of fulfilling.

Pyrogen Testing

As stated in previous comments to ICCVAM (attached),[22] while we appreciate the effort to expand the use of the Monocyte Activation Test (MAT) in order to replace the rabbit pyrogen test (RPT), we are concerned about the rabbit use proposed for the validation study. BioTest has suggested a validation study that includes the RPT and LAL along with the MAT.[23] Inclusion of these assays in parallel is an attempt to address the ICCVAM recommendations for future studies enumerated in the 2008 Test Method Evaluation Report (TMER), section 2.3.[24] BioTest also proposes to include endotoxin and non-endotoxin standards (lipotechoic acid and crude preparations from gram positive bacteria), a pro-inflammatory substance, parenteral pharmaceuticals, biologics, and devices. However, we question the need for parallel LAL and RPT testing given the inability of the LAL to detect non-endotoxin pyrogens and the abundance of existing LAL and RPT reference data available for comparison and extrapolation.
If all the reference standards and classes of products proposed are tested in rabbits, this study could lead to significant animal use. The number of animals who would be consumed by parallel testing is one of the reasons that RPT studies were not conducted as part of the original validation study performed by the ECVAM.[25] Another reason cited by ECVAM is the fact that it is common practice to validate pyrogen tests for every given product. Rather than conducting a massive and animal-intensive validation study, ECVAM opted for a smaller study to demonstrate the general applicability and validity of the methods for regulatory purposes, *leaving validation of the assays for additional pyrogens and product classes up to manufacturers*. This sensible approach should be

[22] White, 2011.
[23] April 7, 2011 letter from BioTest AG to Dr. William Stokes. Available at: http://iccvam.niehs.nih.gov/methods/pyrogen/MAT-2011/CoverLtr-MAT-07Apr2011HK.pdf
[24] National Toxicology Program (NTP); NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM); Availability of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) Test Method Evaluation Report: Validation Status of Five *In Vitro* Available at: http://www.federalregister.gov/articles/2008/11/24/E8-27790/national-toxicology-program-ntp-ntp-interagency-center-for-the-evaluation-of-alternative
[25] European Commission, Directorate General, JRC: Statement on the Validity of In-Vitro Pyrogen Tests. March, 2006.

applied here to prevent the duplicative use of rabbits in an ICCVAM validation followed by a product specific validation. Parallel studies should not be conducted. Instead, ICCVAM and BioSentinel should take advantage of RPTs currently taking place for regulatory purposes and facilitate product specific validation of the MAT. Collection of this data could, over time, fulfill data needs for validation of the MAT.

Strategic Opportunity 4: Develop and Strengthen Partnerships

Under this strategic opportunity, ICCVAM discusses the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), a federally chartered advisory committee for NICEATM and ICCVAM that provides scientific, policy, and practical advice from non-Federal stakeholders. The plan notes in several places that members represent academia, regulated industries, state government agencies, and *animal welfare organizations*. However, only one AWO is represented on the committee, the ASPCA, an organization whose involvement in regulatory testing issues and promotion of nonanimal methods is arguably limited. PETA and PCRM, on the other hand, employ staffs of scientists devoted solely to regulatory testing, most of whom hold advanced degrees in toxicology, molecular and cellular biology, environmental science, and public health, yet attempts to secure representation on the SACATM have been ignored. At a recent ICCVAM meeting, nominations to the SACTM of a PETA scientist from the EPA and FDA were ignored; the nominations for new members instead came directly from a list provided by the executive director of ICCVAM and were not subject to review by other members of ICCVAM. As a federal agency, SACATM's formation falls under FACA regulations, which specify the following:

Agency officials, members of Congress, the general public, or professional societies or current and former committee members may nominate potential candidates for membership. Selection of committee members is made based on the FACA's requirements and the potential member's background and qualifications. Final selection is made by the president or heads of agencies.

Also under this strategic opportunity, the plan mentions the International Cooperation on Alternative Test Methods (ICATM), which has been in existence since 2009. Again, a description of detailed outcomes, goals, or plans is notably absent. How has the existence of ICATM helped ICCVAM accomplish its remit? The development of “international best practices” is listed as a goal not yet accomplished—what are the barriers to accomplishing this goal, three years after its formation? Is it worth the effort? More details on this activity are warranted.

Finally, ICCVAM notes that it will interact with and offer technical assistance to the U.S. representatives on the United Nations Sub-Committee of Experts on the Globally Harmonized System of Classification and Labeling of Chemicals (GHS) to implement revisions and updates to the GHS applicable to new, revised, and alternative test methods.

However, ICCVAM is carrying out an active campaign to prohibit the U.S. from adopting GHS. Adopting GHS for skin and eye irritation would allow for the use of

completely non-animal methods to assess skin irritation using methods that were validated for this purpose by the ECVAM. OSHA has already agreed to adopt the GHS for skin irritation. Yet the executive director of NICEATM and ICCVAM has decided that the U.S. should not adopt GHS and has been campaigning against adoption of GHS despite the fact that this is clearly a regulatory decision outside the purview of ICCVAM or NICEATM. ICCVAM's campaign against GHS also runs counter to OSHA decisions as well as the internal decision processes of both the EPA and the FDA. Adoption of GHS represents one instance in which ICCVAM could actually make a positive impact and completely replace animal testing for skin and eye irritation – which would be in line with the individual assessments of the relevant regulatory agencies.

Summary

In summary, NICEATM-ICCVAM's draft five-year plan reveals the committee's apparent intention to continue playing at best an extremely minor role in the adoption of non-animal test methods while its member agencies and European counterparts do the heavy lifting. The draft retains many of the previous plan's priorities, thus demonstrating the ongoing and alarming lack of ambition and creativity on the part of ICCVAM. Key developments in toxicology are not even considered or adequately discussed, including the AOP concept which is critical to achieving the National Academies' vision for toxicity testing in the 21st century. NICEATM-ICCVAM must promote, rather than oppose, U.S. adoption of GHS and allow meaningful representation of animal welfare organizations on its scientific advisory committee. We once again call upon NICEATM-ICCVAM to address the specific concerns detailed above in the final version of this plan and in its update to its Implementation Plan, which must also set concrete goals and timeframes for gauging progress.

Sincerely,

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Physicians Committee for Responsible Medicine

Attachments:

January 13, 2010 Update of the NICEATM-ICCVAM Five-Year Plan: Request for Comments
Method Review by the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM)
May 29, 2009 letter to Dr. Linda Birnbaum
June 7, 2007 comments to Dr. William Stokes on the Draft NICEATM-ICCVAM 5-Year Plan (2008-2012)
June 9, 2011 letter to Dr. Lori White