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**1. The Role of NICEATM and ICCVAM in Establishing Scientific Confidence in the Use of Tox21 Methods Should be Clearly Delineated**

The Draft 5-Year Plan opens to a promising start outlining four main strategic thrusts. Thrust 1 which discusses the role of NICEATM and ICCVAM to promote the application and translation of innovative science and technology is encouraging – the initial focus describes areas of focus such as high-throughput screening (HTS), biomarkers, computational models, integrated testing strategies (ITS), etc. However, the 5-year plan lacks description of the concrete activities that NICEATM and ICCVAM will actually be engaged in to develop scientific confidence in the relevance and reliability of these advanced methods, which is certainly necessary prior to their use in regulatory programs. Unfortunately, the overall impression from reading through the Draft 5-Year Plan is that ICCVAM is a passive party in the field of Tox21. This is disappointing since the next 5 years are expected to be formative in terms of outlining a framework and context for the development, evaluation and application of alternative, advanced screening methods. The 5-Year Plan seems to position ICCVAM as a body that will react to activities that are driven by other agencies, and not as a central body for leading the effort, across agencies, to coordinate the scientific evaluation of new, improved and advanced alternative methods.

**2. NICEATM and ICCVAM Should Consider Engaging in the Evolution of Validation Strategies for Application to Advanced Screening Methods such as Tox21**

While traditional approaches for test method validation may be difficult to apply to Tox21, ToxCastTM, and related methods, there is a pressing need to establish the reliability of these methods. It's imperative that these new approaches achieve the requisite degree

of scientific confidence so that they can be appropriately used and their results relied on for decision making. There is an opportunity for NICEATM and ICCVAM to engage with the Tox21 collaborators as well as stakeholders in the agencies, academia, private sector and NGO communities, to help define approaches for validation that will be applied to Tox21 and related advanced screening methods. In moving forward to develop the approaches for establishing scientific confidence in these advanced molecular screening assays, ACC offers four recommendations:

**A.** It is not feasible or useful to truly consider validation of Tox21 (or related methods) by itself in the abstract. Indeed, the context and purpose of use must also be considered, and the degree of scientific confidence (validation) will vary in accordance with specific uses. A lesser degree of confidence would be acceptable for priority setting, compared to a regulatory decision leading to restriction of manufacturing or use.

**B.** Rather than an ECVAM/ICCVAM validation framework, adapting both the framework published by (1)[IOM (2010)] and that of the OECD Validation principles for (Q)SARs (2) [OECD, 2007)] would provide a more relevant context to assess the robustness, domain of applicability and utility of Tox21 assays and their generated data.

**C.** Proprietary or uncharacterized assays must be appropriately transparent and enable independent and sufficient scientific scrutiny by peer review of analytical performance (reliability) regardless of the ultimate application of the assays. Analytical performance for priority setting or screening would still require the same level of scrutiny. In this regard, we suggest that development and application of heuristic performance standards would be one way to achieve greater scientific confidence in proprietary assays.

**D.** Knowledge of biological response pathways is a critical component in the validation and interpretation of Tox21 (and related assays and their data). Understanding the mode of action and underlying biology will be essential for the integration of biological relevant assays into hazard and risk assessment and to ensure that the resulting prediction models are both rigorous and fit for their intended purpose. Moreover, it is vital that the domain of the predictive model is adequately defined to ensure that it is applied to both relevant chemicals and human biology.

## 3. Specific Opportunities for Collaboration with European and Asian Validation Entities Should be Described

Despite signing a memorandum of understanding to promote harmonization of test methods with other comparable validation organizations in Europe and Asia, there is no mention of what has been delivered as a result of this initiative nor what will be carried out collaboratively in the future. This leaves the impression of a very US centric focus and may lead to lost opportunities. Given the application of alternatives to whole animal testing globally, there must be some strategic opportunities to work collaboratively with

other comparable bodies or at the very least to outreach and disseminate the activities outside of the narrow focus of ICCVAM' s 15 Member agencies.

**Specific Comments:**

**Page 5:** Sole mention of Adverse Outcome Pathways (AOPs) – although these are not referenced elsewhere or defined. Given ECVAM and OECD's interest in AOPs, and the collaborative activity that is under development by these organizations, it is surprising not to see more emphasis on the efforts being undertaken to develop and evaluate AOPs.

**Page 14:** "ICCVAM' s role is becoming increasingly "entrepreneurial." It's not clear what entrepreneurial means or how this behavior would actually be strategic and not just tactical, or how such entrepreneurial activities will lead to meaningful accomplishments. For example, if ICCVAM accepts any nomination that is submitted, for example, a proprietary method that just replicates an existing non-proprietary method, just to be active, it's hard to see how such an activity would really contribute to the overall mission of ICCVAM.

**Page 15-17:** A description of approaches and tools for regulatory science, Tox21 are discussed but not all related to activities that are being funded and undertaken by other agencies. It is not clear what role or engagement ICCVAM will play in terms of valuating the reliability and performance of the predictive models of EPA's ToxCastTM program, for instance. These pages rather provide a description of what others are undertaking but without any evidence of what connection or interplay that will exist with ICCVAM.

**Page 18:** Toxicology Databases – mention is made of those that have been developed as part of Toxnet – but there is no ontology associated with these databases hence for the purposes of exploiting the data in a form that can help inform the development of alternatives – these offer limited benefit. Where is the link with initiatives such as the OECD Toolbox, eChemPortal or even ACTor? This may be a very productive role for NICEATM and ICCVAM.

**Page 23:** The highlights of ICCVAM appear quite limited in the last 5 years and many appear to be dovetailed to efforts initiated elsewhere. One of the accomplishments listed is the International Collaboration established with the US, Canada, Europe, Japan. However, what if anything has been a tangible output of this collaboration as in years since its formation? No reference is made to what this collaboration has effectively delivered. It appears as though it is a symbolic gesture rather than actually realizing anything specific.

**Pages 24-32:** This section is rather nebulous. It would be considerably more informative to describe more of the "how" rather than the "what."

• Stating that, for example, acute dermal systemic testing will be addressed is one thing – but it curious to see that there is nothing specific about what in vitro tests might be employed or how an AOP may be developed, evaluated or quantified.

• How, if at all, is the work ICCVAM have been undertaking in validating the BG1 Luc estrogen receptor transactivation test linked to EPA's EDSP and EDSP21? The Draft 5-Year Plan for endocrine appears to be divorced from the work of the EPA.

• The plan only mentions monitoring appropriate advances in the area of AOP development, e.g., ITDS for skin sensitization. But this would seem to be an ideal case to connect or collaborate with efforts within OECD in terms of quantifying the AOP for skin sensitization that was developed.

**Page 32:** A description is provided for validation which has some similarities with the proposals suggested by ACC. However, there appears to be no context of how validation as a framework might evolve for the new types of test methodologies, such as Tox21. This is a critical shortcoming of the Draft 5-Year Plan. When concerns are raised that the traditional approach for conducting method validation and demonstrating model predictivity may not be practical for Tox21, ToxCast™ and other advanced screening methods, we recommend the process of validation could largely follow the model presented in the 2010 report from the Institute of Medicine, Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease (1)[IOM, 2010)]. This process consists of: (1) Analytical Validation, considering the analytical performance of an assay; (2) qualification, an assessment of the association of the assay with a molecular initiating event, key event or biomarker associated with the mode of action (MOA); and (3) utilization, a contextual and weight-of-evidence analysis of the specific and possibly quantitative use of the assay based on all available and relevant evidence. We believe a similar approach will be the best path in building the scientific confidence in the use of Tox21 and ToxCast™ assay data for prioritization, screening, and ultimately, hazard prediction and risk assessment.

(1) Institute of Medicine (IOM) (2010) Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease. ISBN: 978-0-309-15129-0.

(2) Organization for Economic Co-operation and Development (OECD) (2007) Guidance Document on the Validation of (Quantitative)Structure-Activity Relationships [(Q)SAR] Models at http://www.oecd.org/officialdocuments/displaydocumentpdf?cote=env/jm/mono(2007)2&doclanguage=en accessed March 30, 2012.