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Date: Tuesday, September 10, 2013 4:23 AM
To: Warren Casey <warren.casey@nih.gov>, "Tice, Raymond (NIH/NIEHS) [E]" <tice@niehs.nih.gov>
Subject: A New Vision and Direction for ICCVAM: Comments from EURL ECVAM on Draft Document

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Document on "A New Vision and Direction for ICCVAM" - Comments from EURL ECVAM

As the EU Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM), we welcome this vision document. By understanding better the direction that ICCVAM and NICETAM want to take, we will hopefully be in a better position to identify sound opportunities for collaboration in the coming years. We also welcome the chance to provide our feedback that we hope you find useful. In summary;

1. We believe that international cooperation is essential to make real progress in, as you say, "exploration of new paradigms for the validation and utilization of alternative toxicological methods". In this context therefore, we would like to see specific reference made to the International Cooperation on Alternative Test Methods (ICATM) and an indication that you will remain a committed partner. In the section, "Increase agency awareness of international 3R efforts" you only mention interaction with the OECD. Besides ICATM, the European Partnership on Alternative Approaches to Animal Testing (EPAA – see http://ec.europa.eu/enterprise/epaa/) could also be an important cooperation partner for ICCVAM/NICEATM.
2. Close involvement of regulatory agencies in priority setting, identifying promising methods and defining projects seems very appropriate indeed. We see some parallels with our own engagement with PARERE - EURL ECVAM's advisory network for Preliminary Assessment of Regulatory Relevance of alternative methods. (see http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/scientific-advice-stakeholders-networks/parere). It would be interesting to examine possibilities for common initiatives and exchange of information where appropriate.
3. You state that in the short-term you intend to focus effort and resources in the area of skin sensitisation. As you know, EURL ECVAM formally released its strategy on skin sensitisation hazard identification/classification in March this year (see http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/replacement-of-animal-testing-eurl-ecvam-releases-its-strategy-for-skin-sensitisation-hazard-identification-and-

classification/?searchterm=None), after consultation with various bodies including ICATM partners. We are currently very active in many aspects of its implementation including - progressing the validation of in vitro methods that reflect key events in the pathway, the compilation of datasets of reference chemicals, the design and evaluation of Integrated Testing Strategies (ITS), and the leading of a drafting group at the OECD on a guidance document on Integrated Approaches to Testing and Assessment (IATA) for skin sensitisation. Of course there is still much to do before we (i.e. the 3Rs community) can deliver complete solutions that have regulatory acceptance. Thus I'm sure the contribution of NICEATM/ICCVAM to this area will be of great value and we look forward to interacting with you as you formulate your own strategy and implementation plan.

4. As you know, in May this year EURL ECVAM published its Recommendation on the 3T3/NRU cytotoxicity assay and its possible use in acute oral toxicity assessment (see http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/replacement-of-animal-testing-eurl-ecvam-releases-its-strategy-for-skin-sensitisation-hazard-identification-and-classification/?searchterm=None). This may have relevance for your intention to, "assess the utility of in vitro assays (e.g. 3T3 NRU) for predicting oral LD50 values". Our conclusions indicate however that simply using cytotoxicity (cell viability/lethality) assays will not suffice. We are currently formulating a strategy in this area and intend to pursue a number of the actions proposed in the 3T3/NRU Recommendation. We would welcome the opportunity to discuss cooperation on this topic, and in particular, how to formulate Weight-of-Evidence and ITS approaches which include complementary sets of property data, including cytotoxicity data.

5. As you begin work on the ICCVAM website, we would welcome the opportunity to identify content that could be cross-referenced with our own website, and vice versa (see http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/replacement-of-animal-testing-eurl-ecvam-releases-its-strategy-for-skin-sensitisation-hazard-identification-and-classification/?searchterm=None). We renewed our site earlier this year but are still working on improving it further. In addition, as you know, within the activities of ICATM we have proposed to lead the development of a revamped TSAR – the Tracking System for Alternative methods towards Regulatory acceptance. We hope that you will continue to support this project since I expect that it will prove to be a very useful information source/system for ICCVAM members and its stakeholders.

6. In relation to your objective to, "achieve broader engagement with the scientific community and stakeholders …", we would be delighted to share our experiences concerning our engagement with ESTAF – EURL ECVAM's Stakeholder Forum (see http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/scientific-advice-stakeholders-networks/estaf-ecvam-stakeholder-forum). We continually seek better ways to effectively communicate our science and to take on-board the ideas and views of the committed 3Rs stakeholder community. We'd welcome the chance to learn more about the various initiatives you mention and to work together on some projects/ideas of mutual interest.

7. Regarding your point that, "the concept of validation needs to be re-considered", and a possible objective on, "changing the concept of validation", we are somewhat concerned that your comments may be interpreted that a major overhaul is needed across the board when it comes to method validation. Although we are very much in agreement with you that as the safety assessment paradigm becomes more knowledge-driven, integrative, and less reliant on animals, organisations like ours need to look for effective and efficient ways to validate emerging methods and approaches to ensure that they are ultimately accepted and used. However we see this more as "an evolution, rather than a revolution" that needs careful consideration and informed international debate. Moreover, as you know, validation has many facets it will never be a case of "one size fits all". Therefore I'm sure that you appreciate that when discussing "validation", we must be clear to distinguish between the 3Ps - Principles, Purpose and Process. We encourage you to raise your concerns and suggestions within ICATM and the OECD (e.g. TG Programme and WNT, and the Hazard Assessment Task Force) to initiate some healthy discussion.

8. We notice that there is no reference made in the document to peer review. Assuming that in the future, ICCVAM/NICEATM will pursue some sort of 'performance evaluation' of newly proposed methods/approaches, we are wondering if there is still an intention on your part to arrange peer-review of the outcome of such evaluations, as a step towards the issuing of final recommendations by NICEATM, ICCVAM, or ICCVAM member agencies? If so, how do you anticipate the process to be arranged? Details on our own peer review process by ESAC – the EURL ECVAM Scientific Advisory Committee, can be found at http://ihcp.jrc.ec.europa.eu/our_labs/eurl-ecvam/scientific-advice-stakeholders-networks/ecvam-scientific-advisory-committee-esac .

Again, many thanks for providing the opportunity to provide feedback and we look forward very much to future cooperation.

Best wishes,

Maurice.

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