Corners

The American Society for Cellular and Computational Toxicology is excited to announce that its 4th annual meeting will be expanded to two days and held in Durham, North Carolina at the Environmental Protection Agency. The meeting, which will be October 1-2, 2015, features an IATA theme: "Integrated Approaches to Testing and Assessment: Promises and Challenges of a More Flexible Approach to Toxicology Testing". Plenary lectures will be provided by Warren Casey, Director of NICEATM, and Craig Rowlands from the Dow Chemical Company. The agenda will also feature invited case study presentations, flash poster presentations, a panel discussion and a social reception. Top submitted abstracts will be selected for oral presentation; abstracts are due July 15. Find more information and register at www.ascctox.org.

The importance of Good Cell Culture Practice (GCCP) to the acceptance and use of *in vitro* methods is incontrovertible; for this reason ASCCT was proud to support and co-sponsor the Johns Hopkins University Center for Alternatives to Animal Testing (CAAT) GCCP for induced Pluripotent Stem Cells (iPSCs) workshop, which took place in Baltimore June 1-3, 2015. Under CAAT leadership the workshop was very productive and will result in an update of published guidance.

Finally, to accomplish its goal of providing opportunities for collaboration and discussion among scientists, the ASCCT has recently made all of its webinars, formerly open only to members, open to all. Members still get priority registration access and can view webinar recordings in perpetuity. Consider becoming a member to access these benefits, find out about new webinars (including the next one on August 5!), and support this vital educational program.

Kristie Sullivan
ASCCT Secretary

CAAT*feed*

Joint Information Day on Biology Inspired Microsystems – Status and Future

CAAT's Transatlantic Think Tank for Toxicology (t^4) was the sponsor (along with Roche, Tissuse and TEDD) of the *Joint Information Day on Biology Inspired Microsystems – Status and Future*, held June 11, 2015 in Berlin. This event brought together renowned experts in the field to share information about the status quo, promises and current shortcomings of microphysiological systems. The event followed a three-day workshop on the topic.

Good Cell Culture Practice (GCCP) for Induced Pluripotent Stem Cells Workshop

CAAT hosted an invite-only workshop on Good Cell Culture Practice (GCCP) for Induced Pluripotent Stem Cells on June 1-3, 2015 in Baltimore. Participants included representatives of ECVAM, EPA, NIH, NCATS, EPA, stem cell banks, and other experts on iPSC. The goal was to update the 2005 GCCP guidelines to include pluripotent stem cells and microphysiological systems. CAAT is currently establishing a secretariat for a GCCP Collaboration to be formed later this year. Contact: David Pamies (dpamies1@jhu.edu)

Webinar: The Human Toxome Project – a Test Case for Pathway Identification by Multi-omics Integration Now Available for On-demand Streaming

CAAT Director Thomas Hartung presented a webinar on the Human Toxome Project, which is funded by an NIH Transformative Research grant (2011-2016) and is focused on developing the concepts and the means for deducing, validating, and sharing molecular Pathways of Toxicity (PoT). Using the test case of estrogenic endocrine disruption, the responses of MCF-7 human breast cancer cells are being phenotyped by transcriptomics and mass-spectroscopy-based metabolomics.

In this webinar, CAAT Director Thomas Hartung presents one of the first specific findings addressing why an integrated biology approach analyzing results from multiple technologies simultaneously can significantly improve interpretation and guide follow up experiments more quickly than mining a single molecular category. In this case, integrating proteomics and transcriptomics data provided a small number of nodes to focus metabolomics validation and demonstrates the practical application of this approach.

Watch the Webinar (free, available for streaming): http://bit.ly/1BKzqRD

CAAT-Europe Director Marcel Leist Interview

CAAT-Europe Director Marcel Leist was interviewed about alternatives on German DRadio Wissen. The interview may be heard here: http://dradiowissen.de/beitrag/leidfrei-forschen-ohne-tierversuche

Thomas Hartung Presents "The Maturing Toolbox of Regulatory Toxicology" at Mid-Atlantic Society of Toxicology Webinar

The Mid-Atlantic Society of Toxicology presented a webinar on "Regulatory Acceptance of Alternative Methods: Current Status and Future Directions" on May 14, 2015. Thomas Hartung spoke on "The Maturing Toolbox of Regulatory Toxicology." Other speakers included George DeGeorge (MB Research Labs), Warren Casey (NIEHS) and Rodger Curren (IIVS).

Discover Magazine Covers CAAT's "Brain-on-a-Chip" Research

The June 2015 issue of *Discover Magazine* article, "Building a Full-Blown Human Body-on-a-Chip," mentions the work of the CAAT research team on "miniature brains." CAAT Director Thomas Hartung hopes to build a "brain-on-a-chip" that can eventually plug into the Interrogator, a project under development at Harvard's Wyss Institute that aims to combine ten chips representing different organ systems.

New Paper (and two Invited Responses) in Archives of Toxicology: MPTP's Pathway of Toxicity Indicates Central Role of Transcription Factor SP1

This paper, by CAAT's Alexandra Maertens, Thomas Luechtefeld, Andre Kleensang and Thomas Hartung, explores the use of weighted gene correlation network analysis (WGCNA) to extract an initial network from a small microarray study of MPTP toxicity in mice. This analysis both captures much of the known biology of MPTP toxicity and suggests several candidates for further study. Furthermore, the analysis strongly suggests that SP1 plays a central role in coordinating the cellular response to MPTP toxicity. The paper shows a way forward to deduce pathways from untargeted 'omics data.

Full Article via Springer: http://bit.ly/1RtXA4H

There were two guest editorials in response to the paper:

Developing Tools for Defining and Establishing Pathways of Toxicity by Melvin E. Andersen, Patrick D. McMullen and Daniel Krewski, see http://bit.ly/1LzCyjo

From Smoking Guns to Footprints: Mining for Critical Events of Toxicity Pathways in Transcriptome Data by Jörg Rahnenführer and Marcel Leist (CAAT-Europe), see http://bit.ly/1Nh1Q70

Meeting of European 3Rs Centers

CAAT-Europe participated in the "Meeting of European 3Rs Centres" hosted by EURL ECVAM at the European Commission's Joint Research Centre (JRC) on April 21-22, 2015. Participants from across the EU met to share information on their organizations and to present their activities on a variety of innovative ways to achieve impact in the 3Rs. Specific areas discussed included the identification of priorities to reduce animal use in biomedical research; communication and dissemination of knowledge and information on the 3Rs; education and training at undergraduate, postgraduate and professional levels; validation of methods towards their use in regulatory safety assessment; and understanding, for example, how *in vitro* models (e.g., engineered tissue) can be developed and promoted as a key enabling biotechnology to stimulate innovation and growth in a variety of sectors. A number of opportunities for closer cooperation between centers were identified.

François Busquet Presents at 3Rs Workshop in Romania, Interviewed on French Radio

CAAT-Europe Policy Coordinator François Busquet was invited to present at the 3Rs Workshop "Finding Opportunities in the Area of Alternative Methods to Animal Testing for Romania" on June 5, 2015 at the Universitatea de Ştiinţe Agricole şi Medicină Veterinară in Cluj-Napoca, Romania. The workshop represented a first attempt to initiate discussions, to map existing activities, and to identify opportunities in the area of alternative methods to animal testing in Romania.

Busquet was also interviewed on national French Radio. You can listen to the streaming audio here: http://bit.ly/1Nh1LQL

Workshop on "Dynamic modeling of metabolic responses in neurotoxicology (Dynametox)"

This workshop, hosted by CAAT, was held May 11-12, 2015, in Konstanz, Germany and was hosted by CAAT. Participants included the Max-Delbrück Center Berlin, Forschungszentrum Jülich and the University of Konstanz.

Mardas Daneshian Radio Interview on GM Animals

CAAT-Europe CEO Mardas Daneshian was interviewed on SWR2 on "From Guinea Pigs to GM Mice – Genetically Modified Animals in Medical Research." The interview (in German) aired on June 10, 2015.

Paul Locke Speaks at "21st Century Understanding of Chemicals" in Washington, D.C.

CAAT's U.S. Policy Director Paul Locke spoke at "21st Century Understanding of Chemicals", held in the Rayburn House Office Building in Washington, D.C. on April 6, 2015. This briefing explored issues between chemical innovation and policy frameworks that, in some cases, are decades old. The event was sponsored by the American Chemical Society Science and the Congress Project with ACS Corporation Associates and the American Political Science Association.

Thomas Hartung Featured Speaker for "Whole Blood Assay (MAT) – Detection of Broad Spectrum of Pyrogens & Examples of Medical Device Testing" Webinar

CAAT Director Thomas Hartung was the featured speaker for a webinar on the "Whole Blood Assay (MAT) – Detection of Broad Spectrum of Pyrogens & Examples of Medical Device Testing" on April 9, 2015. The webinar presented a closer look at the whole blood assay, non-endotoxin pyrogen detection and pyrogen testing in medical devices and was sponsored by EMD Millipore & BioPharma Reporter.

The webinar is available at: http://bit.ly/1J2O725

Recent Publications

Efremova, L., Schildknecht, S., Adam, M. et al. (2015). Prevention of human dopaminergic neurodegeneration in an astrocytes co-culture system allowing endogenous drug metabolism. *Br J Pharmacol*, May 18. http://dx.doi.org/10.1111/bph.13193

Luechtefeld, T., Maertens, A., McKim, J. et al. (2015). Probabilistic hazard assessment for skin sensitization potency by dose-response modeling using feature elimination instead of quantitative structure-activity relationships. *J Appl Toxicol*, Jun 5. http://dx.doi.org/10.1002/jat.3172

Maertens, A., Luechtefeld, T., Kleensang, A. and Hartung, T. (2015). MPTP's pathway of toxicity indicates central role of transcription factor SP1. *Arch Toxicol 89*, 743-755.

Smirnova, L., Seiler, A. E. M. and Luch, A. (2015). microRNA Profiling as Tool for Developmental Neurotoxicity Testing (DNT). *Current Protocols in Toxicology* (pp. 20.9.1-20.9.22). Hoboken, NJ, USA: John Wiley & Sons, Inc.

News from the President of ECOPA on behalf of its Board

The next General Assembly will take place at the EUSAAT – Linz Congress on September 20-23, 2015. Date, time and room will be announced.

The secretary of ecopa attended the opening of ROCAM (ROmanian Center for Alternatives Methods) on June 5 in Cluj. More information is available on ROCAM's website. http://rocam.usamvcluj.ro/index.php/events

Ecopa has been formally accepted as a stakeholder by ECHA and is represented by Costanza Rovida, who attended the 10th ECHA Stakeholders' Day. A summary is given below:

Participation in the 10th Stakeholders' Day at ECHA (Helsinki)

In spite of the urgency derived from the final implementation of the CLP Regulation, with abrogation of the previous directives (June 1, 2015) and the upcoming final deadline for registering substances according to the REACH regulation (May 31, 2018), ECHA demonstrated to be focused on the promotion of alternative test methods, with specific references in almost all of their presentations. This is probably the consequence of the Ombudsmen decision,[1] which found that ECHA was failing to actively promote the use of alternative methods to comply with the REACH provision (December 11, 2014). ECHA has now promised serious commitment in reducing unnecessary animal testing.

During the meeting, there was explicit assurance that ECHA will be more careful in the future in evaluating whether *in vivo* tests are really necessary by also automatically controlling registrants who submit *in vivo* tests without going through the testing proposal procedure. During the presentations there was also explicit mention that cosmetic ingredients should not be tested on animals.

Read-across and grouping are important opportunities to waive new *in vivo* tests for the characterization of substances. However, submitters should not act with superficiality and both approaches must be duly justified. Almost all of the controlled dossiers were non-compliant in this sense. This is why ECHA has recently published the Read-Across Assessment Framework (RAAF),[2] which describes the internal tool for the examination of predictions, based on read-across of the human health properties of chemical substances in the context of the REACH Regulation. This should guide the submitters in understanding whether their approach will be accepted. Unfortunately, this document is only theoretical, with no practical examples, and the application remains cumbersome.

Noteworthy, revision 6.0 of IUCLID is coming soon. It will contain dedicated pages for inserting *in vitro* results from skin and eye irritation study reports. Hopefully, this will encourage registrants to avoid *in vivo* tests, which is absolutely possible considering that there are enough validated *in vitro* methods. According to an investigation performed throughout the dossiers that were submitted in the latest years, on average only half of the new tests were *in vitro* tests. Replying to a specific question, ECHA promised that Annex VIII of REACH will be revised, cancelling the request for the *in vivo* skin/eye irritation test, which is misleading as the availability of validated methods makes replacement possible with full compliance of the registration dossiers. The next meeting is expected in October 2015.

For further details, please contact Costanza Rovida (costanza.rovida@chimici.it).

News from the ECOPA members

FRANCOPA

The joint meeting between the management group and the experts of the French platform dedicated to alternative methods took place on June 9.

The working group on teaching proposed a questionnaire aimed at identifying and understanding the needs of regulatory toxicologists in terms of their lack of knowledge on alternative methods. According to the answers provided by the toxicologists a specific training course could be devised.

Didier Hoffschir (French ministry of research) and Christophe Joubert (CEA) provided their feedback on the way French ethical committees work and evolve. J-P. Clot (OPAL) presented the results of a French audit aimed at describing and quantifying animal use in higher education. According to his recommendations FRANCOPA will play a role in establishing an inventory of alternative methods and in diffusing information on these tools. F. Busquet (CAAT-Europe, ecopa's secretary) provided an overview of the recent European and international activities in the field of alternative methods. Issues related to the "Stop Vivisection" Europe-

[1] http://bit.ly/1GE8v8Z

[2] echa.europa.eu/documents/10162/13628/raaf_en.pdf

an Citizens' Initiative and on the recommendation of the European Ombudsman for ECHA were discussed. A. Kienzler (EURL-ECVAM) gave an overview of ECVAM activities. The activities of the European Union Reference Laboratory prompted questions on the role of national platforms, and the machinery of the networks PARERE and NETVAL. The operational meaning of "validate model" was also briefly discussed. I. Fabre (ANSM) provided information on the new FRANCOPA report on the state-of-the-art in the field of alternative methods in France.

The afternoon was largely dedicated to a workshop whose aim was to discuss the different strategies that researchers adopt in order to select the most appropriate models for their investigations (*in vivo*, *ex vivo*, *in vitro*). The opportunities and limits that characterize alternative methods and *in vivo* methods were discussed also with respect to the societal reaction to the recent European Citizens' Initiative.

IPAM

The exhibition project entitled "Science and Awareness: A Journey Inside the 3Rs" will be hosted at the Università la Sapienza in Rome, Italy on September 25 - October 2, 2015. It is organized by IPAM (the Italian Platform for Alternative Methods) and is intended as a journey to get to know the scientific value of the 3Rs. It is aimed at outlining the theoretical and practical evolution of research methods based on the principles of Replacement, Reduction and Refinement in various fields of biomedical research.

The 2nd LIFE-EDESIA workshop in collaboration with IPAM, the Italian Platform of Alternative Methods, and CAAT Europe will be held in Ranco, Italy on July 20-22, 2015. It is titled "The role of *in vitro* functional assays for the assessment of endocrine disruptors/EDCs." Invited participants are representatives from EFSA, EURL ECVAM, EPA, FDA and major expert scientists in the area of endocrine disruption activity of chemicals. The workshop report will be published in ALTEX.

SET

The German Consensus Platform SET within ecopa is, as in former years, supporting the European 3Rs Congress EUSAAT 2015 (http://eusaat-congress.eu) to be held from September 20-23 in Linz, Austria. In addition, to promote sustainability of the 3R principles of Russel & Burch into science of the 21st century, SET is funding a special "Young Scientist Travel Award (YSTA)" program to support participation of as many young scientists as possible from different countries to the congress. The best YSTA submissions will be presented as short oral presentations in a special "Young Scientists Session."

SET will also hold an expert workshop "Translational Aspects of *In Vitro* and *In Vivo* Models for Inflammatory Diseases" as a satellite event to the Congress on September 23-24, 2015. Since participation in the workshop is restricted to invitees, whenever possible, the presentations of the workshop experts will be integrated in the EUSAAT 2015 Congress Program, and thus be made available to a large audience.

NORECOPA

The Norwegian consensus-platform Norecopa, in collaboration with the University of Bergen, arranged a two-day workshop in May entitled Systematic Reviews and Harm-Benefit Assessment of Animal Experiments, with lecturers from SYRCLE, the RSPCA and Norecopa. There were 34 participants from 7 countries. The workshop clearly demonstrated how important it is to train researchers in how to conduct efficient literature searches of the large bibliographic databases such as MEDLINE, and how to locate 3R resources. More information is available on http://norecopa.no/systematic-reviews.

Norecopa held its Annual General Meeting in Oslo on June 5. Guest speakers were Dr. Lynne Sneddon, Liverpool University, who spoke on "Detection and alleviation of pain in fish" and Professor Eddie Clutton from Edinburgh University, whose presentation was entitled "Pain management after surgery: are we good enough?" The presentations will be made available at http://norecopa.no/arsmoter. A round table discussion was organized to discuss how to reduce the number of animals used in the development and testing of fish vaccines. The panel included representatives from industry, the regulatory authorities and academia. Norecopa's Board will follow up the conclusions from these discussions by arranging an expert group meeting this autumn to formulate specific recommendations for international progress in this area.

Norecopa's annual 3R-Prize was awarded on June 5 to Professor Stig Larsen, Norwegian University of Life Sciences, for his work in developing a refinement of Response Surface Pathway Design (RSP). His modification of the RSP design has been shown to reduce the need for animals in LD_{50} testing by over 50% while at the same time increasing the accuracy of the result. His presentation at the award ceremony can be read here: http://norecopa.no/files/Development-of-RSP-Design.pdf

A new national Regulation on the use of animals in research will come into force in Norway on July 1, along with a new system for processing applications from researchers and for monitoring animal research. This will bring Norway into full compliance with the requirements of EU Directive 2010/63.

EUSAAT

European Society for Alternatives to Animal Testing

News from EUSAAT

Changes in the EUSAAT Board

Since the publication of the last EUSAAT news in ALTEX, 3/14, several changes have occurred on the EUSAAT Board. First, on October 30, 2015 Dr Ursula G Sauer resigned as Secretary General (SG) and also from the EUSAAT Board and later, on May 29, 2015, Dr Eleonore Haltner-Ukomadu resigned as Vice President and also from the EUSAAT Board. As interim solution, Horst Spielmann is acting as "provisional SG" and the successors of Eleonore and Ursula will have to be elected at the AGA 2015 during the EUSAAT2015 congress in Linz this September.

EUSAAT members are encouraged to serve on the EUSAAT Board and to submit their candidatures during the next two months to the SG Horst Spielmann or any other Board member.

EUSAAT2015 congress in Linz on September 20-23, 2015

Despite the changes in the EUSAAT Board the remaining EUSAAT Board members managed to proceed with the planning of the annual EUSAAT2015 congress, which as usual will be held in Linz, Austria. In addition, EUSAAT signed an organization contract with our former SG Helmut Appl from "appl communications & consulting e.U." Since Helmut has successfully managed all of the previous ZET/MEGAT/EUSAAT congresses in Linz, we are quite confident that EUSAAT2015 will also be a memorable event, in particular since it is the only international 3Rs congress in 2015. Moreover, an extremely supportive international group of experts in the Scientific Committee (SC) has drafted an attractive program for the congress.

The highlights of the EUSAAT2015 congress are shown in the DRAFT program below. We are happy that due to generous sponsoring, we are for the first time offering the "Young Scientists Travel Award" to encourage the participation of young scientists.

The EUSAAT Board and the SC are happy that institutions devoted to the 3Rs have taken the initiative to hold two Satellite meetings right after the congress:

#1 The EUSAAT 2015 Practical Training Course on Alternative Methods Assessment of *In Vitro* Eye Irritation potential – focusing on methods accepted for the regulatory purposes, and

#2 The SET WORKSHOP "Translational Aspects of *in vitro* and *in vivo* Models for Inflammatory Diseases."

DRAFT Program of the EUSAAT2015 congress (as of June 22, 2015)

- **New technologies: systems biology, -omics technologies, 3D models**
  coordinators: **Ellen Fritsche**, IUF Düsseldorf, Germany & **Horst Spielmann**, FU Berlin, Germany
  - Stem cells
  coordinators: **Jürgen Hescheler**, U Cologne, Germany & **James Adjaye**, U Düsseldorf, Germany
  - Multi-organ-chips (MOC), human-on-a-chip
  coordinators: **Uwe Marx**, TissUse & TU Berlin, Germany & **Dimitri Sakharov**, Russian Acad. Sciences, Russia

- **International progress in 3Rs research & Global cooperation on implementing the 3Rs**
  coordinators: **Dave Allen**, ASCCT, USA, **Hajime Kojima**, JSAAE & JaCVAM, Japan & **Troy Seidle**, HSI, Canada

- **Replacement – new approaches**
  coordinators: **Mardas Daneshian**, CAAT Europe, U Konstanz, Germany, **Candida Nastrucci**, U Rome Italy & **Stefanie Schindler**, AnimalfreeResearch, Germany & Switzerland

- **Predictive toxicology**
  - QSAR & Read Across
  coordinators: **Karel de Raat**, ECHA, Finland & **Matthias Herzler**, BfR, Germany
  - Risk assessment based on the AOP concept
  coordinators: **Ellen Fritsche**, IUF, Germany, **Anna Bal-Price**, JRC, Italy & **Tzutzuy Ramirez**, BASF, Germany

- **Specific toxicological endpoints**
  - Repeated-dose toxicity
  coordinators: **Klaus R. Schröder**, BioMed-zet Life Science Austria & **Joachim Wiest**, cellasys Germany
  - Inhalation
  coordinators: **Samuel Constant**, Epithelix, Switzerland & **Rodger Curren**, Institute for In Vitro Sciences, USA
  - Nanotoxicology
  coordinators: **Robert Landsiedel**, BASF, Germany & **Claus-Michael Lehr**, HIPS, Germany
  - Bio-barriers
  coordinator: **Claus-Michael Lehr**, Helmholtz-Institute for Pharmaceutical Research Saarland (HIPS), Germany
  - Skin sensitization
  coordinators: **Joao Barroso**, EURL ECVAM, Italy, **Helena Kandarova**, SETOX & MatTek IVLSL, Slovakia & **Robert Landsiedel**, BASF, Germany

- **Efficacy and safety testing of drugs, biological and vaccines**
  coordinators:**Tuula Heinonen**, SCCT & FICAM, Finland, **Coenraad Hendricksen**, InTaVacc & Utrech University, NL & **Gerhard Püschel**, U.Potsdam, Germany

- **Disease models *in vivo* and *in vitro***
  ***- In vivo* – CRISPR/Cas-induced structural variants**
  coordinators: **Horst Spielmann**, FU Berlin & **Malte Spielmann** MPI Molecular Genetics & Charité, Germany
  ***- In vitro* – human cell and tissue models**
  coordinators: **Manfred Liebsch**, ecopa, Germany & **Peter Reinhardt**, CRTD, TU Dresden, Germany

- **Ethical and legal issues**
  coordinators: **Herwig Grimm**, Messerli Inst, Austria & **Roman Kolar**, Academy for Animal Welfare, Germany

- **EU Directive 63/2010 on the protection of animals used for scientific purposes**
  coordinators: **Susanna Louhimies**, EU Commission, Belgium & **Herman Koëter**, OHP & ACT, Italy & NL

- **Refinement & welfare, culture of care, best practice approaches, avoidance of severe suffering**
  coordinators: **Susanna Louhimies**, EU Commission, Belgium, **Katy Taylor**, BUAV, UK & **Christa Thöne-Reinecke**, Veterinary School, FU Berlin, Germany

- **3Rs in academia and education**
  coordinators: **Ellen Fritsche**, IUF Duesseldorf, Germany, **Marcel Leist**, CAAT Europe, Germany, **Candida Nastrucci**, U Rome, Italy & **Monika Schaefer-Korting**, Inst. Pharmacy FU Berlin, Germany

- **"Young scientists" session & Free communications**
  coordinators: **Lucia Li**, FU Berlin, Chinese U Hong Kong, Germany & China, **Manfred Liebsch**, ecopa, Germany & **Helena Kandarova**, SETOX & MatTek IVLSL, Slovakia

News from NICEATM and ICCVAM

EPA Requests Comment on Use of High-Throughput Assays for EDSP

The U.S. Environmental Protection Agency (EPA) requests comment on a plan to incorporate validated ToxCast/Tox21 high-throughput assays and a computational model as an alternative to three Tier 1 tests used in its Endocrine Disruptor Screening Program (EDSP) to assess estrogenic activity. Use of these alternative methods will accelerate the pace of screening, decrease costs and reduce animal testing.

The EPA plan was developed by EPA and NICEATM scientists and is described in detail in the journal Environmental Science and Technology (Browne et al., 2015; http://dx.doi.org/10.1021/acs.est.5b02641). The EPA request for comment was published June 19 in the U.S. *Federal Register*, available at http://www.gpo.gov/fdsys/pkg/FR-2015-06-19/pdf/2015-15182.pdf. Comments on the plan are requested by August 18.

ICCVAM Holds Public Forum

ICCVAM convened a Public Forum on May 27 at the National Institutes of Health (NIH) in Bethesda, Maryland. The Public Forum gave attendees opportunities to discuss alternatives for chemical and product safety testing with ICCVAM members.

Fifteen ICCVAM members representing 10 member agencies were joined at the Public Forum by 12 public participants and nearly 100 webcast viewers. Public participants represented interest groups including industry, academia, and animal welfare organizations. Key points raised included requests for more transparency in reporting animal use by industry, more training for regulators on available non-animal methods and strategies, and better communication to the public of the science behind non-animal methods.

Presentations given at the Public Forum, public comments and a link to a recording of the webcast are available at http://ntp.niehs.nih.gov/go/iccvamforum-2015.

EPA Updates Guidance on Non-Animal Eye Irritation Tests

EPA updated its guidance document describing a non-animal testing scheme for assessing eye irritation potential of EPA-registered antimicrobial cleaning products. The testing scheme uses the bovine corneal opacity and permeability, EpiOcular, and cytosensor microphysiometer assays to identify Toxicity Category I, II, and III eye irritants for antimicrobial cleaning products. The guidance can be downloaded from the EPA website at http://1.usa.gov/1HdEBM7. General information about pesticide registration is available at http://www2.epa.gov/pesticide-registration.

USDA Updates Guidelines for Validation of *In Vitro* Potency Assays

The U.S. Department of Agriculture Center for Veterinary Biologics (USDA CVB) recently updated Veterinary Services Memorandum No. 800.112, "Guidelines for Validation of *In Vitro* Potency Assays." This memorandum provides guidance concerning the information manufacturers should provide when submitting new potency assays for veterinary vaccines and other biological products to the CVB. These guidelines apply to *in vitro* assays used to determine the potency of such products, and provide a framework for designing *in vitro* potency assays and the studies needed to validate those assays. Use of *in vitro* assays may replace, reduce or refine animal use for this purpose.

Veterinary Services Memorandum No. 800.112 and other recently published CVB documents are available at http://1.usa.gov/1Jii2X0; click on "Veterinary Biologics" and then "Newly Published Information."

Upcoming Meetings and Workshops

– ICCVAM's advisory committee, the Scientific Advisory Committee on Alternative Toxicological Methods, will hold its annual meeting on September 2 at the National Institute of Environmental Health Sciences in Research Triangle Park, NC. Preregistration is required to attend the meeting in person; the meeting will also be webcast. An agenda, other materials, and links to register are available at http://ntp.niehs.nih.gov/go/32822.
– The 4th Annual Meeting of the American Society for Cellular and Computational Toxicology will be held October 1-2 at EPA in Research Triangle Park, North Carolina. The theme of the meeting is "Integrated Approaches to Testing and Assessment: Promises and Challenges of a More Flexible Approach to Toxicity Testing." The program will include presentations of case studies that apply integrated approaches to testing and assessment. Plenary speakers will include NICEATM Director Warren Casey speaking on "Moving Beyond One Test: Leveraging the Whole Toolbox for Integrated Decision Strategies," and Craig Rowlands of The Dow Chemical Company speaking on "Chemicals and Risk: New Approaches to Current Practices." There will also be a poster session and oral presentations selected from submitted abstracts. More information is available at http://www.ascctox.org/meetings.cfm.
– NICEATM is organizing a best practices workshop on strategies and recommendations for using *in vitro* to *in vivo* extrapolation in chemical screening and risk assessment. The workshop will be held February 17-18, 2016, at EPA in Research Triangle Park. Information on the workshop will be posted at http://ntp.niehs.nih.gov/go/ivive-wksp-2016 as it becomes available.

Recent NICEATM Interactions

– Nicole Kleinstreuer, a NICEATM support contractor, gave a presentation titled "Integrated computational approaches to the assessment of skin sensitization potential of chemicals" at an April 21 symposium for regulators at the California Environmental Protection Agency. The focus of the half-day symposium was on advances in skin sensitization determination using *in vitro* and *in silico* methods.
– NICEATM helped to organize a June 1-2 workshop on "Good Cell Culture Practices for Induced Pluripotent Stem Cells" (iPSC) hosted by the Center for Alternatives to Animal Testing. The goal of the workshop was to produce a guidance document outlining consensus standards on the use of iPSC. This document is in preparation and will be submitted for publication later this year.
– Dr Casey presented updates on NICEATM and ICCVAM activities at ASIATOX 2015 on June 23-26 in Jeju City, South Korea. While in Korea, he attended a coordination meeting of the International Cooperation on Alternative Test Methods (ICATM) and an International Workshop on Validation Management for Alternative Test Methods, hosted by KoCVAM.

IIVS
Institute for In Vitro Sciences
Advancing Science & Animal Welfare Together

IIVS News & Views

Industry and Regulatory Collaboration Pays Off for Animals

The US Environmental Protection Agency (EPA) has updated a policy which will result in fewer products required to be tested in the eyes of rabbits. The policy is the outcome of a multi-year project between industry, the EPA and IIVS. Coordinated by The Accord Group, the project successfully identified three non-animal tests which can be used in place of the rabbit test to determine the eye irritation potential of commonly used household cleaning products. The majority of cleaning products in the US do not undergo pre-market registration. However, those which carry antimicrobial claims are considered pesticides and animal testing is required by the EPA before they can be sold. The update expands the use of the Bovine Corneal Opacity and Permeability Assay for labeling US EPA Category III eye irritants. "This policy illustrates the constructive way that industry and the regulatory community can work together to replace the use of animals in testing," comments Dr Rodger Curren, current CEO of IIVS and lead scientist on the project. "It took a lot of commitment and resources from industry and the EPA to turn this concept into a reality." It is expected that these tests will provide useful information on the eye irritation of other types of products and result in even less animal testing in years to come.

Workshop Presented to PETA on the Current Science of Non-animal Test Methods

In May, IIVS organized a workshop for scientists from the People for the Ethical Treatment of Animals' (PETAs') Regulatory Testing Department in Washington, D.C. to give updates on various non-animal testing methods currently being used by industry. The overall aim of the workshop was to provide PETA scientists with a deeper practical understanding of the methods, and to discuss how the current science can be used to provide the best information on a substance's safety without the need for additional animal testing. IIVS has presented similar workshops for other animal protection organizations as well as industry groups and regulatory agencies as part of our mission to educate stakeholders on the current science behind the use of non-animal testing methods. The meeting began with a general presentation of IIVS's mission, current projects, and the history of collaboration with PETA. IIVS Study Directors presented on methodologies that have OECD Test Guidelines focusing on eye irritation, skin irritation and corrosion, skin sensitization, phototoxicity, and skin penetration. Special attention was given to discussing unique case studies and troubleshooting measures. PETA scientists visited the IIVS laboratory the day after the presentations for a tour and live demonstrations of some of the methods discussed. The meeting concluded with a summary and wrap-up question and answer session with all of the IIVS presenting scientists. Participants from both organizations felt this was a successful meeting and look forward to continued collaborations in the future.

Mid-Atlantic Society of Toxicology (MASOT) Webinar Presentation

Dr Rodger Curren, CEO of IIVS, spoke on the status of regulatory acceptance of *in vitro* methods during a May webinar organized by the Mid-Atlantic Society of Toxicology (MASOT). The well-attended webinar began with a general overview of alternative methods. Information on the regulatory acceptance of these methods was shared with participants, particularly focusing on recently-validated tests. The webinar concluded with thoughts on up-and-coming methods and current and future regulatory challenges. Abstracts from the webinar presentations are available on the MASOT website at http://www.masot.org/groups/rc/MidAtlantic/index.asp.

Cosmetic Design SkinCare Ingredient Online Event

IIVS participated in this year's SkinCare Ingredient Online Event as a bronze sponsor. This event, the fifth of its kind sponsored by Cosmetics Design, was designed to bring the attendees the latest consumer and market insights, scientific developments and technical innovation concerning skin care ingredients. IIVS Study Director Dr Kimberly Norman presented a webinar on the use of *in vitro* test methods for safety and efficacy testing on ingredients and also participated in the round table discussion at the close of the conference where general information on the global acceptance and use of *in vitro* methods was discussed. Additional webinar recordings and informational handouts on *in vitro* toxicology testing were available to participants in the event. The online event portal will remain open until September 2015. Please visit the event website (http://skincare-ingredients.com/) to gain access to recordings of the day's presentations and additional information available in the resources area.

IIVS Continues Outreach Activities in China

Through the support of its Industry Council for the Advancement of Regulatory Acceptance of Alternatives (ICARAA) and contributors to our International Outreach Program, IIVS sent Dr Rodger Curren, CEO, Ms Erin Hill, President, and Dr Quanshun Zhang, Senior Scientist, to several meetings in China to present the scientific merits of non-animal test methods to key scientists in the country. Dr Curren gave a well-received presentation at the National Institute for Drug Control (NIFDC) in Beijing on key concepts when designing or evaluating assay validation. This was followed by participation in the "4th Annual Workshop on Alternatives" in Guangzhou. The meeting was organized by Guangdong CIQ and Sun Yet San University. Approximately 50 participants attended the IIVS lecture on *in vitro* methods for skin sensitization, a timely topic given the recent issuance of OECD test guidelines. IIVS also participated in the "Workshop on Cosmetic Risk Assessment and Alternatives to Animal Testing" organized by the Guangdong CDC and Unilever. This meeting drew over 200 attendees from industry, academia and representatives from several provincial and national government institutions such as the Chinese FDA (CFDA). Dr Curren again spoke on validation concepts while Dr Zhang focused his presentation on the technical aspects of currently used *in vitro* test methods. IIVS has received several comments from regulatory officials in China that our efforts are resulting in greater interest in *in vitro* methods within the community. IIVS will continue supporting China's efforts to move toward the use of non-animal test methods by helping China's scientists gain momentum to advance regulatory science through training and sharing of our experiences.

Further Advances in *In Vitro* Model Development for Regulatory Respiratory Toxicology

IIVS hosted a Society of Toxicology ancillary meeting to discuss the recommendations from a workshop held last December which addressed the development and standardization of *in vitro* models for use in tobacco regulatory science. The purpose of the December workshop was to bring together experts and stakeholders (e.g. academia, industry, regulatory, and *in vitro*/*ex vivo* model development) to generate a focused path forward to identify and further develop *in vitro* methods which might be useful to industry and the regulatory community. The SOT session summarized the areas of scientific focus discussed during the meeting: inflammation and oxidative stress, ciliary dysfunction and ion transport, goblet cell hyperplasia and mucus production, and parenchymal/bronchial tissue destruction and remodeling. A technical workshop was convened at IIVS in June to further explore the current state of the science and agree on parameters for the development of standardized protocols for evaluating the relevant endpoints. Additional discussion and collaboration on these methods will continue and a manuscript with proceedings is available at the IIVS website (www.iivs.org).

As a result of the successful first meeting, a second open workshop will be held April 4-6, 2016 entitled: "In Vitro Exposure Systems and Dosimetry Assessment Tools for Inhaled Tobacco Products". If you are interested in learning more about IIVS' work in respiratory toxicology please contact Dr Holger Behrsing (hbehrsing@iivs.org)

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