Corners

The American Society for Cellular and Computational Toxicology (ASCCT) recently held its 6th Annual Meeting at the headquarters of one of its founding organizations, the Institute for In Vitro Sciences. Meeting attendees participated in several oral presentation sessions, a poster session, panel discussion, awards ceremony, and mentoring event, all focused on the development and implementation of alternative, nonanimal toxicology science and policy. As in 2016, the meeting was held at a time and place to coincide with the Science Advisory Committee for Alternative Toxicological Methods (SACATM), an advisory group for the US-based Interagency Coordinating Committee for the Validation of Alternative Methods. This structure fits well with ASCCT's mission to increase the cooperation and dialog between toxicologists from government, industrial, academic, and non-profit organizations.

The meeting started September 21 with a focus on acute systemic toxicity thanks to a pair of plenaries touching on policy and scientific advances and challenges. Anna Lowit from the US EPA presented *EPA-OPP's Initiative to Modernize the Acute "6-Pack"* and Dan Wilson from Dow Chemical Company presented a *Progress Report on Efforts to Replace Acute Systemic Toxicity Tests with Mechanistic Alternative Approaches*. After several talks from submitted abstracts on acute systemic toxicity, updates on FDA CFSAN efforts to modernize regulatory toxicology and the establishment of a new Canadian alternatives center were provided by Suzanne Fitzpatrick from the US Food and Drug Administration and Charu Chandrasekera from the Canadian Centre for Alternatives to Animal Methods, respectively.

The day ended with the awarding of the Tox21 Student Award to Wenyi Wang from Rutgers University for her work titled *Mechanistic Evaluation of Chemicals that Induce Oral Acute Toxicity by Mitochondrial Membrane Disruption: Big Data Profiling and Analysis*; the Edward Carney Award for Predictive Toxicology was given to Ellen Garcia from Virginia Tech for her presentation *Characterization of two lung cell lines for use in cell division focused, single-cell toxicity assays*.

Under the Lautenberg Chemical Safety Act (LCSA), the EPA is tasked with creating a strategic plan for developing and implementing methods which reduce and replace vertebrate animal testing. The second day of the meeting began with a plenary providing a *Progress Report on Development of a Strategic Plan to Reduce, Refine or Replace Use of Vertebrate Animal Testing Under the Lautenberg Act* from Gino Scarano of US EPA. Another platform presentation session followed Dr Scarano's presentation, and the day was rounded out with an active and engaging closing panelist and audience discussion to provide EPA feedback and advice, and discuss views, roles, and responsibilities of all stakeholders involved in Lautenberg Act implementation.

Thanks to all who attended, spoke, and participated in the planning! A full report will be put together for publication in the coming months, and all are welcome to join in the planning for the 7th Annual Meeting in the fall of 2018.

CAAT*feed*

Next Generation Humane Science Award – Open for Applications

The Next Generation Humane Science Award is available annually to young scientists in the US to acknowledge and encourage researchers who focus on replacing the use of animals in experiments. The 2017 award will be a prize of up to $9,000 to recognize the work of one young scientist, or may be shared among two or more young scientists.

Application deadline: November 30, 2017
More information: http://caat.jhsph.edu/humanescienceaward.html

Thomas Hartung and CAAT Featured at Future Port Prague

Future Port Prague is a one-day conference and festival that aims "to help people and businesses in our region better understand ... not just the technology, but the deeper societal changes that will require a rethinking and rewiring of our business models and environments, our education systems, and most importantly, our own mindsets."

Thomas Hartung spoke on "The Future of Healthcare."
Future Port Prague website: https://www.futureportprague.com/

CAAT-Europe's François Busquet Spoke at European Parliament's Intergroup on the Welfare and Conservation of Animals

François Busquet, Europe Policy Coordinator at the Center for Alternatives to Animal Testing-Europe (CAAT-Europe), spoke at the European Parliament's Animal Welfare Intergroup Session's second presentation on current dynamics in 3Rs science and policy worldwide.

Busquet said: "*The current dynamics in 3Rs (replacement, reduction, and refinement) for laboratory animals used for scientific purposes are globally positive. In spite of research and regulatory improvements in other parts of the world, such as the USA and Canada, the European Union still spearheads and gives the tempo when it comes to 3Rs*."

The European Union is setting the pace within the legal frameworks of REACH, the complete ban on the sale of cosmetics developed through animal testing, and the Directive 2010/63/EU on the protection of animals used for scientific purposes.

The EU is also at the forefront of research with initiatives like EU-ToxRisk, an integrated European flagship program driving mechanism-based toxicity testing and risk assessment, and the Innovative Medicines Initiative (IMI).

Some Member States like the Netherlands, the United Kingdom, Italy and Sweden have their own national strategy on 3Rs science.

Video now available: Thomas Hartung on Alternative Approaches to Food Safety Assessments

Thomas Hartung discusses CAAT's work on read-across and the need for non-traditional approaches to food safety testing as part of the workshop: *State of the Science on Alternatives to Animal Testing and Integration of Testing Strategies for Food Safety Assessments*, co-hosted by U.S. Food and Drug Administration, Center for Food Safety and Applied Nutrition (CFSAN), and ILSI North America Technical Committee on Food & Chemical Safety. The workshop was held at the FDA in College Park, MD on February 28, 2017.

Full video: https://www.youtube.com/watch?v=_yJhn_JdDiY&feature=youtu.be

in3 project kicks off

CAAT-Europe is a partner in the Marie Skłodowska-Curie Innovative Training Networks project "An integrated interdisciplinary approach to animal-free chemical and nanomaterial safety assessment" – in3. The in3 project aims to significantly further the development of animal-free chemical and nanomaterial (NM) safety evaluation by creating a scientific and training program aimed at integrating human *in vitro* testing with computational approaches. The project focuses on human induced pluripotent stem cell (hiPSC) derived tissues, including liver, kidney, brain, lung and vasculature and utilizes mechanistic toxicology, quantitative adverse outcome pathways, biokinetics, cheminformatics and modelling approaches to derive testable prediction models. The in3 project, started in January 2017, had its kick-off meeting on October 4-5, 2017 in Amsterdam, The Netherlands.

CAAT-Europe's Johanna Nyffeler at the US EPA

Former CAAT-Europe collaborator Johanna Nyffeler joined the US EPA to further develop new toxicology approaches.

CAAT-Europe interaction with US National Institute of Health's (NIH) National Toxicology Program (NTP)

CAAT-Europe associates Tanja Waldmann and Johanna Nyffeler were invited to attend a NDT meeting entitled *Integrated Testing Strategies for Developmental Neurotoxicity Workshop*. This workshop took place from September 25 to 28 in facilities of US National Institute of Environmental Health Sciences (NIEHS) in Research Triangle Park, NC. Besides Johanna Nyffeler's active role as moderator of the session on "*In*

vitro high content screens for neurotoxicity," she gave a presentation on "Migration of human neural crest cells as functional endpoint to screen for developmental neurotoxicity". Tanja Waldmann's presentation was about "Assessment of neurite outgrowth in LUHMES and stem cell derived peripheral neurons." Both test systems presented screened the National Toxicology Program's (NTP) 80-compound library and could show that they are suitable for screening purposes, that there is a high hit confirmation rate, and that the tests allow sorting of toxicants according to potency.

CAAT-Europe's Costanza Rovida Presented "New Approach Methodologies (NAMs) for Biomedical Research" at University of Milano

On September 13, Costanza Rovida from CAAT-Europe held a conference at the University of Milano on "New Approach Methodologies (NAMs) for Biomedical Research."

The event was organized by the Centre for Complexity and Biosystems in the Physics Department of the University in Milan and provided a general outline of the NAMs applied in the different sectors of biomedical research, with particular focus on the AOPs (Adverse Outcome Pathways) and Tox21c.

Symposium on Investigative Toxicology at EUROTOX 2017

September 11, 2017, Bratislava, Slovakia

Investigative toxicology is a relatively young discipline mainly focusing on pharmaceutical safety assessment. It sees itself complementary to regulatory toxicology. Whereas regulatory toxicology's boundaries are set by international guidelines and its methods and technologies have matured over the last decades, investigative toxicology is more driven by early screens and *ad hoc* mechanistic elucidation moving safety assessment from a descriptive to a mechanistic understanding and an improved human translation.

To advance the discipline of investigative toxicology, a group of 14 Europe-based investigative toxicology scientists from pharmaceutical industry (AstraZeneca, Bayer, Boehringer Ingelheim, GSK, Janssen, Lundbeck, Merck, Novartis, Novo Nordisk, Orion Pharma, Roche, Sanofi, Servier and UCB-Biopharma) have formed the Investigative Toxicology Leader (ITL) Forum. This forum aims at an exchange of pre-competitive knowledge among the companies and an interaction with relevant experts from academia and regulatory bodies. The objective is to elaborate robust, reliable and accepted investigative toxicology concepts for decision-making for early safety-related attrition, de-risking, and mechanistic elucidation of effects. Another key aspect is the translation of *in vitro* to *in vivo* mechanistic data. Furthermore, the adoption of new technologies (e.g., microphysiological systems) and assays into the drug discovery back-bone is targeted by the forum.

The forum teamed up with CAAT-Europe in order extend the range of the interaction also to other sectors and to establish synergies within a broader network of relevant experts. The CAAT-Europe ITLF collaboration prompted a think tank meeting (July 2017) and a symposium that took place within the EUROTOX 2017 conference on September 11, 2017.

Thomas Hartung presented on "European Think Tank on Investigative Toxicology". Full details may be found here: http://www.eurotox2017.com/monday/

One-day Training Course on Development of Human Immortalized and Induced Pluripotent Stem Cells for *In Vitro* Disease Modeling and Toxicity Testing

September 10, 2017, Bratislava, Slovakia

ESTIV and CAAT joined forces to organize a one-day training course on "Development of human immortalized and induced pluripotent stem cells for *in vitro* disease modeling and toxicity testing" at Eurotox 2017.

The course provided a unique opportunity to gain insight on challenges and opportunities for the development and standardization of human immortalized and iPSCs from different organs.

Lectures included:

- Immortalization of human cells, by Regina Grillari (BOKU, Austria)
- Neuronal differentiation of human pluripotent stem cells lines, by András Dinnyes (Biotalentum, Hungary)
- Human pluripotent stem cells for cardiac disease and safety pharmacology, by Robert Passier (Leiden University Medical Centre, The Netherlands)
- Induced pluripotent stem cell-derived cellular systems for *in vitro* disease modelling and toxicity testing, by Giorgia Salvagiotto (Cellular Dynamics, UK)
- Bioengineering next-generation stem cell culture technology, by Nikolce Gjorevski (EPFL, Switzerland)
- Good cell culture practices on human stem cells, by Thomas Hartung (CAAT, USA)

Other presentations at EUROTOX 2017 by CAAT included:

- *Good cell culture practices on human stem cells*: Thomas Hartung
- *Good Cell Culture Practice for stem cells and stem-cell-derived models*: David Pamies
- *Read-Across-based QSAR for REACH*: Thomas Hartung
- *The new toxicity tools to advance drug development*: Thomas Hartung

CAAT/CAAT-Europe posters at EUROTOX 2017

- *Metabolic flux analysis in human dopaminergic neurons under toxicant stress*: Johannes Delp
- *Comparison of toxicity patterns of 19 compounds across 16 organ-specific* in vitro *test methods*: Alice Krebs
- *CAAT-Academy: Hands-On Training in 3Rs: An endeavor to fill in the gap*: Ilija Prachkovski

2017 Charles River Laboratories Excellence in Refinement Award Presented to Hanno Würbel, PhD

Begun in 2005, the Charles River Laboratories' Excellence in Refinement Award, sponsored by Charles River's Commitment to Humane Animal Research Through Excellence and Responsibility (CHARTER) Program, in cooperation with the Johns Hopkins Center for Alternatives to Animal Testing (CAAT), honors an individual who has made an outstanding contribution to the development, promotion and/or implementation of refinement alternatives. This award is based on the conviction that the humane care of laboratory animals is both a moral imperative and a scientific necessity. The award, which includes $5,000 to further the recipient's scientific endeavors, is presented during the World Congress on Alternatives and Animal Use in the Life Sciences.

We are happy to announce the 2017 Charles River Laboratories Excellence in Refinement Award was presented to Dr Hanno Würbel. Dr Würbel was chosen to win this award for his refinements in the housing of laboratory animals. His research has shown that environmental enrichment can be used in mice to improve the animals' wellbeing without reducing the reproducibility of experimental results. His expertise in this area of research is considered unique worldwide, some of his activities include refinements in phenotypic plasticity, animal welfare, and the validity of animal experiments.

Dr Würbel currently is a Professor and Chair of Animal Welfare at the Veterinary Public Health Institute at the University of Bern, Switzerland.

CAAT/CAAT-Europe at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences

CAAT was well-represented at the 10th World Congress on Animal Use in the Life Sciences, which took place August 20-24 in Seattle. Presenters and talks included:

- *Young Scientists in Action (YOU WC10): Follow the 3R Career Paths*: Thomas Hartung
- *Awareness of the economic potential of non-animal approaches mirrored by governmental funding schemes*: Mardas Daneshian
- *Gene environment interaction for autism in a brain organoid model*: Lena Smirnova
- *Dopaminergic cell recovery in an* in vitro *3D model to study Parkinson's disease*: Georgina Harris
- *From Microphysiological to Micropathophysiological Systems*: Thomas Hartung
- *3D Neural Models to Study Toxicity and Disease*: Helena Hogberg
- *Application of systematic reviews for transparent, objective and consistent test methods comparison to inform regulatory decisions about new test methods acceptance*: Sebastian Hoffmann
- *CAAT-Academy: Hands-on Training in 3Rs: A tentative to fill in the gap*: Francois Busquet
- *Deriving Pathways of Toxicity from -Omics Data: Endocrine Disruptors as a Case Study*: Alex Maertens
- *Good Cell Culture Practice (GCCP 2.0)*: David Pamies
- *Read-Across-based QSAR for REACH*: Thomas Hartung
- *CRO interface to implement and use non-animal New Approach Methodologies (NAMs) for regulatory purposes: Challenges, Opportunities and Threats*: Costanza Rovida
- *READ-Across in EUToxRisk Toxicity Testing and Risk Assessment for the 21st Century*: Thomas Hartung
- *Survival guide for performing good 3Rs lobbying within the EU policy arena*: Francois Busquet
- *An introduction to International Biocompatibility Testing of Medical Devices*: Sebastian Hoffmann

Other recent presentations

6th Annual Meeting of the American Society for Cellular and Computational Toxicology
September 21-22, 2017;
Gaithersburg, MD, USA
Automated Read-Across for REACH
Thomas Luechtefeld

Northland Society of Toxicology Fall Meeting
September 29, 2017;
Twin Cities of Minneapolis/St. Paul, MN, USA
Opening keynote: *21st Century Alternative Methods for 21st Century Safety Sciences*
Thomas Hartung

Launch and Inaugural Strategic Visioning Workshop of the Canadian Centre for Alternatives to Animal Methods/Validation of Alternative Methods at University of Windsor, Canada
October 2-3, 2017, Windsor, ON, Canada
Opening keynote: *Science of Animal Experimentation*
Thomas Hartung

CBTox – 20th Congress of the Brazilian Society of Toxicology
October 7-9, 2017, Goiana, Brazil
Opening keynote: *Strategies of the 21st Century Toxicologyfor a Safer and More Sustainable World*
Thomas Hartung
Read-Across
Thomas Hartung

Upcoming Events

Progress in Refinement: Enhancement of Scientific Integrity and Animal Well-Being

November 30, 2107
Baltimore, USA

This one-day meeting will include talks on a number of topics, including: social housing, pain assessment and management, environmental enrichment, noninvasive imaging, and scientific implications for rigor and reproducibility. Recipients of CAAT's Science-based Refinement Award will present on their work. The meeting will also honor CAAT's Director of Science Strategy, Joanne Zurlo, who is retiring.

Contact: jderita1@jhu.edu

CAAT Academy 2017 Hands-on Training Program in Europe

The 2017 CAAT Academy Hands-on Training sessions, which are all based in Europe, include:

CAAT Academy – Tubitak
November 2-3, 2017
2D & 3D liver and skin regulatory models
Istanbul, Turkey

CAAT Academy – Epithelix
November 16-17, 2017
In Vitro Lung Models
Geneva, Switzerland

CAAT Academy – MIMETAS
November 16-17, 2017
Current Applications of Organs-on-a-Chip for the Pharmaceutical Industry
Leiden, The Netherlands

Website: http://www.caat-academy.org

Recent Publications

Eskes, C., Boström, A.-C., Bowe, G. et al. (2017). Good cell culture practices & in vitro toxicology. *Toxicol In Vitro*, Epub ahead of print. doi:10.1016/j.tiv.2017.04.022

Hartung T. (2017). Perspectives on in vitro to in vivo extrapolations. *J Appl In Vitro Toxicol*, Epub ahead of print. doi:10.1089/aivt.2016.0026

Ramirez, T., Strigun, A., Verlohner, A. et al. (2017). Prediction of liver toxicity and mode of action using metabolomics in vitro in HepG2 cells. *Arch Toxicol*, Epub ahead of print. doi:10.1007/s00204-017-2079-6

Leist, M., Ghallab, A., Graepel, R. et al. (2017). Adverse outcome pathways: opportunities, limitations and open questions. *Arch Toxicol*, in press.

Nyffeler, J., Dolde, X., Krebs, A. et al. (2017). Combination of multiple neural crest migration assay to identify environmental toxicants from a proof-of-concept chemical library. *Arch Toxicol*, Epub ahead of print. doi:10.1007/s00204-017-1977-y

Pallocca, G., Nyffeler, J., Dolde, X. et al. (2017). Impairment of human neural crest cell migration by prolonged exposure to interferon-beta. *Arch Toxicol*, Epub ahead of print. doi:10.1007/s00204-017-1966-1

Schildknecht, S., Di Monte, D. A., Pape, R. et al. (2017). Tipping points and endogenous determinants of nigrostriatal degeneration by MPTP. *Trends Pharmacol Sci 38*, 541-555. doi:10.1016/j.tips.2017.03.010

Skardal, A., Murphy, S., Devarasetty, M. et al. (2017). Multi-tissue interactions in an integrated three-tissue organ-on-a-chip platform. *Sci Rep 7*, 8837. doi:10.1038/s41598-017-08879-x

van Ravenzwaay, B., Jiang, X., Luechtefeld, T. and Hartung, T. (2017). The threshold of toxicological concern for prenatal developmental toxicity in rats and rabbits. *Regul Toxicol Pharmacol 88*, 157-172. doi:10.1016/j.yrtph.2017.06.008

EUSAAT

European Society for Alternatives to Animal Testing

Election of the EUSAAT Board and the AC

The AGA 2016 decided on August 25, 2016 in Linz to hold the AGA 2017 during EUROTOX in Bratislava/Slovakia and to hold the election of the Board and of the Audit Committee (AC) electronically prior to EUROTOX. The EUSAAT AGA 2017 was later scheduled for September 11, 2017 at EUROTOX in Bratislava.

Organization of the electronic election of the EUSAAT Board and the AC

EUSAAT members were invited by the SG to serve as candidates for the elections of the EUSAAT Board and AC on July 10, 2017. All candidates signed an agreement form and provided their CVs.

The electronic voting of the EUSAAT Board and of the Audit Committee (AC) was conducted from August 15 to September 6, 2017. The voting procedure was managed by Association House (AH), a subsidiarity of the congress organizer (CRO) Guarant International, who organized WC9 and EUROTOX 2017.

Details of the electronic voting procedure were fixed in a contract with AH. AH invited EUSAAT members to participate in the electronic voting procedure and sent several reminders to EUSAAT members to ensure a high participation in the voting.

The following EUSAAT members agreed to serve on the Election Commission (EC): Christiane Hohensee (D), Dagmar Jirova (CZ), Claus-Michael Lehr (D) and Klaus-Rudolf Schröder (A).

Results of the electronic election of the EUSAAT Board and AC

The AH provided the Election Commission (EC) and the SG with the results of the election on September 7, 2017. The participation of EUSAAT members in the elections was 47%, which is unusually high. All members of the EC approved the results of the election and they were presented to the AGA in Bratislava.

However, at the AGA, it was brought to the attention of the Board that according to Austrian law electronic ballots must be signed by each voter. Owing to this formal error, the AGA decided to annul the results of the election and to repeat them with signed ballots.

The AGA also suggested some changes to the number of votes for each position of the officers of the EUSAAT society (1 vote for president, 1 vote for secretary general, 2 votes for the vice presidents (2), 3 votes for the audit committee and 4 votes for regular board members). Moreover, the AGA decided that in the new election the applications shall be addressed directly to the election committee (EC) and that the EC shall manage the election. Dagmar Jirova, who attended the AGA and is a member of the EC, volunteered to serve as coordinator of the elections.

Terms and conditions for repeating the electronic election of the EUSAAT Board and AC

The electronic election of the EUSAAT Board and AC will be repeated as soon as possible and the results will have to be approved in an "Extraordinary General Meeting" of the EUSAAT society.

Until the new EUSAAT Board and AC have been approved, the current EUSAAT Board will have to manage the society but is not allowed to sign new contracts or start new activities. It will be the main task of the new Board to plan and organize the EUSAAT 2018 congress.

18th European Congress on Alternatives to Animal Testing EUSAAT 2018

The EUSAAT 2018 congress is scheduled for September 23-26, 2018 in Linz. The following topics and others will be considered in the program:

- Advanced technologies: systems biology, -omics technologies, stem cells
- 3D models & multi-organ-chips (MOC), human-organ-chips (HOC)
- International progress in 3Rs research – Global cooperation on implementing the 3Rs
- Replacement – new approaches
- Predictive toxicology & risk assessment
- Specific toxicological endpoints: oral & repeated-dose toxicity, inhalation toxicity, sensitization, reprotox (mEST & hEST), carcinogenesis, nanotoxicology & bio-barriers
- REACH – meeting the 2018 deadline
- Efficacy and safety testing of drugs, biologicals and vaccines
- Disease models using human cells, tissues and organs
- Advanced GMO models – CRISPR/cas *in vivo* & *in vitro*
- Ethical and legal issues & Dir 63/2010/EU update
- Refinement & welfare, culture of care, best practice approaches, avoidance of severe suffering
- 3Rs in education and academia
- "Young scientists" session – Free communications

Horst Spielmann
SG EUSAAT

EU-ToxRisk

The EU-ToxRisk project is very much driven by regulatory demands and regulatory authorities. The idea behind EU-ToxRisk, which was specified by its funding agency, the European Commission, aims at the implementation of non-animal toxicological methodologies especially for regulatory purposes. The project itself both engages and is advised by regulatory authorities, i.e., ECHA and US EPA.

In line with this, the case study (CS) concepts, the CS results, and also the project's AOPs are supervised by regulatory agencies. At the end of the project's second year, the CS results will be communicated to EURL ECVAM's Network for Preliminary Assessment of Regulatory Relevance (PARERE) for evaluation with regard to their validity and whether they are fit-for-purpose for regulatory use. The recommendations of the PARERE network will be discussed with EU-ToxRisk at a meeting on November 28 in the facilities of EURL ECVAM in Ispra, Italy.

On the same day, OECD's IATA Case Study Project discusses the set-up, the quality and performance criteria behind the EU-ToxRisk CS concept in Paris, France. The project's AOPs are discussed with the OECD AOP working group, which will meet 30 consortium representatives on October 23 and 24 in Leiden, The Netherlands. This workshop intends to train the consortium partners in OECD's weight of evidence approach and to give feedback on the set up of the project's AOPs.

Within EU-ToxRisk, nine CS are defined, some of these related to the topic of read-across. Currently, data is being generated in the different human cell models that represent the project's target organs, i.e., liver, kidney, lung and neuronal system, in relation to repeated dose toxicity (RDT) testing and development and reproductive toxicity (DART) testing. A huge number of data points has already been collected with work ongoing.

Computational models for prediction of experimental substance concentrations in EU-ToxRisk test systems are in place. These will advance the translational efforts involving PBPK modeling. Also, advanced model systems, including diseased human steatotic liver spheroids, were established.

In addition to the EU-ToxRisk CS, the concept of exploratory studies (ES) is already implemented. ES follow the same vision as the CS: ES are intended to provide the necessary information to allow regulatory toxicology decisions on the basis of *in vitro* methods and to define the limits of this approach. ES could be defined as "case studies light", i.e., a fast and easy entry into studies that will be terminated if a milestone is not reached or that can transition to the status of a full CS. Moreover, ES allow small project questions to be answered that do not require a full CS but are still important for progress. A third application is to provide show cases to stakeholders of EU-ToxRisk performance and technology in order to attract interest, e.g., for joint CS. An example of the concept is ES1: Here the main question is whether a new AOP for developmental toxicity can be defined on the basis of gap junction changes induced by toxicants, and whether such a key event (KE) would be beneficial for a KE-based test battery. If this can be shown for a limited set of compounds (e.g., polychlorinated biphenyls), then the ES may be expanded to a CS.

The project was presented at the 10th World Congress for Alternatives and Animal Use in the Life Sciences, which took place from August 20 to 24 in Seattle, USA. During this congress the concept was presented exemplified by the parabene case study within the session on "International 3Rs Cooperation" as well as within an EU-ToxRisk dedicated satellite meeting.

EU-ToxRisk was also present at the EUROTOX 2017 conference held from September 10 to 13, 2017 in Bratislava, Slovakia. Bob van the Water presented an update on the project within the session on "Hands-on risk assessment in the 21st century: reports from the front line". The project was also present with a booth, which raised lively interest.

Mardas Daneshian

NTP
National Toxicology Program
U.S. Department of Health and Human Services

ICCVAM Advisory Committee Comments on Roadmap Proposal

About 40 participants attended the September 18-19 meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) meeting at the National Institutes of Health in Bethesda, Maryland.

Meeting participants provided feedback on a strategic roadmap for new approaches to evaluate the safety of chemicals and medical products. While offering a number of specific suggestions to consider as the roadmap is finalized, committee members praised both the roadmap document itself and the work that has already been done toward achieving its goals. This was the last in a series of meetings to solicit public input on development of the roadmap document due to be published in December.

Presentations from the SACATM meeting are available on the National Toxicology Program (NTP) website at https://ntp.niehs.nih.gov/go/8202. Video recordings of the meeting are available on the National Institutes of Health videocast website. The recording of the September 18 session is available at https://videocast.nih.gov/summary.asp?Live=26073&bhcp=1, and the September 19 recording is available at https://videocast.nih.gov/summary.asp?Live=26077&bhcp=1.

SACATM meets annually to advise NICEATM, ICCVAM, and the director of the National Institute of Environmental Health Sciences regarding statutorily mandated duties of ICCVAM and activities of NICEATM. The next meeting of SACATM will be held September 5-6, 2018, at the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina.

BioMed21 Workshop Considers Pathway-based Approach to Disease

NICEATM and the Human Toxicology Project Consortium co-organized a June 27-28 workshop, BioMed21: A Human Pathway-based Approach to Disease and Medicine.

This workshop focused on how data can be used to develop a better understanding of human biology. Such knowledge is needed to develop new approaches for drug development that can identify both potentially effective and potentially toxic drugs before conducting expensive animal and human tests.

Workshop participants spent almost half of the two-day workshop in breakout sessions. Issues considered included experimental design, data sharing, institutional biases that discourage change, and the roles of basic researchers and funding agencies in this effort.

Presentations and a summary of the workshop are available on the Human Toxicology Project Consortium website at https://humantoxicologyproject.org/biomed-21-workshops/biomed-21-us-workshop/.

World Congress Highlights Tox21 Progress

Progress achieved in the first decade of the U.S. federal interagency Tox21 program was highlighted at the Tenth World Congress on Alternatives and Animal Use in the Life Sciences in Seattle, August 20-24.

In a scientific session on the future of Tox21, NTP Biomolecular Screening Branch Acting Chief and ICCVAM member Richard Paules, Ph.D., discussed NTP's role in the future of Tox21. The session also included updates from the other Tox21 partner agencies.

Paules and NICEATM Deputy Director Nicole Kleinstreuer, Ph.D., highlighted how approaches developed through Tox21 can help identify chemicals that could cause cancer. Other NICEATM presentations demonstrated NTP computational tools that can help scientists interpret the large amounts of data generated by Tox21 studies.

NICEATM is applying methods developed through Tox21 and other approaches to reduce and eliminate animal use for acute toxicity testing required by regulatory agencies. NICEATM Director Warren Casey, Ph.D., co-chaired the satellite workshop Towards Elimination of the Acute Toxicity "Six-Pack." The workshop was organized by NICEATM and the National Centre for the Replacement Refinement & Reduction of Animals in Research.

A full list of NICEATM and ICCVAM presentations at the World Congress is available at https://ntp.niehs.nih.gov/go/820400.

NICEATM and ICCVAM Scientists Play Key Roles at ASCCT Annual Meeting

NICEATM staff highlighted ongoing efforts to reduce and replace the use of animals in toxicology testing at the September 21-22 annual meeting of the American Society for Cellular and Computational Toxicology (ASCCT) in Gaithersburg, Maryland.

In a platform presentation, NICEATM Deputy Director Kleinstreuer described a stem cell-based approach to assess the potential for chemicals to cause developmen-

tal toxicity. Other presentations by Shannon Bell, Ph.D., and Agnes Karmaus, Ph.D., who work for NICEATM contractor ILS, described NICEATM data resources for developing and evaluating new testing approaches and detailed an analysis of *in vivo* data variability in acute oral toxicity studies.

Activities of ICCVAM members were also highlighted at ASCCT. The focus of the meeting's first day was "New Horizons in Acute Toxicology." Under this topic, ICCVAM Co-chair Anna Lowit, Ph.D., of the U.S. Environmental Protection Agency (EPA) Office of Pesticide Programs gave a keynote presentation on EPA efforts to replace animal use for required pesticide testing. Later in that day's program, ICCVAM member Suzanne Fitzpatrick, Ph.D., of the U.S. Food and Drug Administration (FDA) described FDA collaborations to use tissue chip platforms for chemical safety testing. The second day of the meeting focused on implementation of the recent Lautenberg Chemical Safety Act. ICCVAM member Louis Scarano, Ph.D., of the EPA Office of Pollution Prevention and Toxics, discussed the process for developing a strategic plan to address requirements in the act to reduce, refine, or replace animal use for testing.

A full list of NICEATM and ICCVAM activities at ASCCT is available at https://ntp.niehs.nih.gov/go/826687.

USDA Exemptions Help Reduce Live Animal Use in *Leptospira* Vaccine Potency Testing

Leptospirosis is a transmissible bacterial disease of animals and humans caused by infection with any of the pathogenic members of the genus *Leptospira*. The organism is shed in the urine and milk of infected animals and may cause symptoms of renal and hepatic disease, which can be fatal. Disease transmission to man and animals is reduced by the vaccination of cattle, swine, and dogs. In light of this, the potency of these vaccines must be tested by law.

In April, the U.S. Department of Agriculture – Animal and Plant Health Inspection Service – Center for Veterinary Biologics (USDA-APHIS-CVB) issued CVB Notice 17-06, "Option to Remove Back-titration Hamsters from *In Vivo* Potency Tests for Leptospira Serogroups Pomona and Grippotyphosa." This notice permits the removal of back-titration hamsters when potency testing vaccines containing *L. pomona* and *L. grippotyphosa* in accordance with 9 CFR 113 §101-104. This exemption to the codified test can reduce animal use up to 50% for these serogroups. CVB Notice 17-06 along with the 2015 CVB Notice 15-13, "Option to Remove Back-titration Hamsters from In Vivo Potency Tests for Leptospira Serogroups Canicola and Icterohaemorrhagiae" are available on the USDA-APHIS website at: http://bit.ly/2gstqcz.

CVB Notice 17-06 is the latest action in a continuing effort by USDA, an ICCVAM member agency, to reduce the number of hamsters required for potency testing of leptospirosis vaccines. In 2013, APHIS issued Veterinary Services Memorandum No. 800.102, which permitted the use of the *in vitro* ELISA test developed by CVB as a complete alternative to live animal usage required under 9 CFR 113 §101-104. CVB provides supplemental assay methods for *in vitro* testing using the ELISA test. All of these documents are available on the NICEATM website at http://bit.ly/2gOSh7p.

Recent NICEATM Publications

- A review in the September issue of the journal *Environmental Health Perspectives* describes how EPA uses adverse outcome pathway (AOP) and toxicity pathway frameworks in its Endocrine Disruptor Screening Program. The review, co-authored by NICEATM Director Casey, describes how these frameworks help to establish biologically plausible links between endocrine-active mechanisms and apical responses when those end points are not measured in the same assay. The review is available at https://ehp.niehs.nih.gov/ehp1304/.
- NICEATM Deputy Director Kleinstreuer coauthored three articles in a special issue of *Reproductive Toxicology* that focused on developmental angiogenesis. The three articles describe projects conducted with EPA and other collaborators that use high throughput screening assays to identify and characterize potential vascular disrupting chemicals. Other articles in the issue describe basic research into the mechanism of angiogenesis and new alternative models for identifying potential vascular disrupting chemicals. The June issue of *Reproductive Toxicology* (volume 70, pages 1-140) can be accessed at http://www.sciencedirect.com/science/journal/08906238/70.

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

Observation Spots Open for 2018 IIVS Practical Methods Workshop

Observation spots are available for IIVS' annual training workshop. During the four-day program, participants will gain the information and expertise to integrate non-animal test methods into their testing programs. Participants will attend lectures given by IIVS scientists and get experience in lab through observation. Learn more and register at http://www.iivs.org.

Chinese FDA and IIVS Re-affirm Their Collaboration for Non-animal Tests

Bo Li, Director General of the CFDA's National Institute for Food and Drug Control (NIFDC) and Erin Hill, President of US based, non-profit Institute for In Vitro Sciences, Inc. (IIVS), signed a Memorandum of Understanding (MOU) to bring non-animal test methods to China for the regulation of cosmetics and ingredients. The move re-affirms and expands a three-year partnership between the NIFDC and IIVS.

Read the full press release at http://www.iivs.org.

Collaborative Effort Aims to Replace Rabbit Test for Personal Lubricant Products

A first-of-its-kind collaborative project is underway to find a non-animal test method to replace the rabbit vaginal irritation test for personal lubricants. The U.S. Food and Drug Administration (FDA) gave the project a green light as part of the agency's program aimed at modernizing the tests used to develop and evaluate medical devices.

The work of the lubricant industry, the Institute for In Vitro Sciences (IIVS), the PETA International Science Consortium Ltd., and the Consumer Healthcare Products Association (CHPA) follows efforts to show that animal testing for lubricants can and should be replaced by non-animal methods, in part because rabbits and humans have very different physiologies.

Read the full press release at http://www.iivs.org.

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