News from the American Society for Cellular and Computational Toxicology

This fall, ASCCT members participated in a webinar on EURL ECVAM's Approach to the Validation of Alternative Methods. Dr Valerie Zuang, coordinator of the EURL ECVAM validation workflow, presented EURL ECVAM's validation workflow, including information on the regulators' network (PARERE), stakeholder involvement, and its scientific peer review process (ESAC). Dr Zuang also reviewed EURL ECVAM recommendations and strategy documents, discussed the test methods which are currently in the validation pipeline, and gave an overview of international activities at the OECD and with ICATM. Members can access a recording of the webinar for free on the ASCCT web site.

The 2nd Annual ASCCT Meeting, *The Future is Here: Practical Application of Emerging Scientific Tools* was just held October 31 at the National Institutes of Health in Bethesda, MD, USA. The theme of the meeting aimed to integrate the development of cutting-edge tools with current regulatory needs. The morning plenaries featured Donald Ingber of Harvard's Wyss Institute, presenting recent work using "organs on a chip" models for drug development and toxicity testing. Thomas Knudsen followed with an overview of the *Virtual Embryo Project*, an effort to develop predictive *in vitro* and *in silico* tools to assess the potential developmental toxicity hazards of chemicals.

These two plenaries were followed by a moderated panelist discussion featuring regulatory, industry, and NGO representatives. After a lunchtime poster session, members gave talks selected from submitted abstracts. These four presentations demonstrated the diverse portfolios of research taking place within the ASCCT membership.

The meeting concluded with the annual business meeting and a cocktail hour. Please see the next issue for a full conference report, and allow us to extend our appreciation to the 2nd Annual Meeting sponsors: the Alternatives Research and Development Foundation, the Center for Alternatives to Animal Testing (CAAT) at JHU, the Institute for In Vitro Sciences, Research Institute for Fragrance Materials, Inc., the Physicians Committee for Responsible Medicine, and SciKon Innovation Inc.

For more information on ASCCT activities and programs, or to become a member, visit our web site at: http://www.ascctox.org

Kristie Sullivan
Secretary, ASCCT
http://www.ascctox.org

CAAT*feed*

t4 Workshop: Tox-21c in practice: Determining the most appropriate point-of-departure based on *in vitro* toxicity data

The use of cell cultures in toxicity testing of chemicals has the potential to provide a detailed picture of the changes of many parameters at once. Even if these changes show a clear concentration-effect relationship, care must be taken in interpreting the results in view of their relevance to the compound's toxicity. Most likely, the sensitivity of these detailed studies will be much higher than what can be derived from the interpretation of apical endpoints in an animal study, e.g., due to the lack of compensatory/homeostatic processes usually working *in vivo*. The question is then: when is a change related to an adverse effect, and when should a change be interpreted as falling within the boundary of the physiologically "normal" adaptive or homeostatic range? The workshop, held June 12-14 in Utrecht, The Netherlands brought together a group of experts from areas of *in vitro* toxicology, systems biology, pathophysiology, and structure-activity relationships to discuss this matter and develop recommendations. A workshop report is under preparation.

t4 Workshop: Integrated Testing Strategies

This workshop, held July 8-10 in Ranco, Italy, was based on the Food for thought … paper Hartung, T., Luechtefeld, T., Maertens, A., and Kleensang, A. (2013). Integrated testing strategies for safety assessments. *ALTEX 30*, 3-18.

Co-organized with BASF, IFRA, RIFM, and ESTIV, the workshop focused on the example of skin sensitization. About 30 experts discussed how to progress in this prime example field in which 19 different alternative methods have been evaluated over the last few years and ITS are starting to emerge. A workshop report is under preparation.

Refinement Program

Beyond regular information and communication (Altweb to the general public and to AALAS as the professional umbrella organization) and the Science-based Refinement Awards, CAAT is entertaining a Refinement Working Group (CAAT-industry), with a secretariat supported by the Klingenstein Foundation. Twelve mainly pharmaceutical companies in the US and seven on the European side have so far joined these efforts. Recent events include:

1. Enhancing 3Rs in Toxicology Studies
This workshop on July 10, 2013 was held in conjunction with the IQ Consortium 3Rs Leadership group at the US Food and Drug Administration to increase dialogue between the agency and the pharmaceutical industry with CAAT as an honest broker. Topics included:
- Advancing animal welfare in toxicology studies
- Non-study design elements focusing on various aspects of refinement including environmental enrichment
- Reduction and refinement in animal studies and optimization strategies for animal studies with emphasis on alternatives to nonhuman primates in the safety evaluation of biotechnology products, reduction in the numbers of animals used, and refinement of blood sampling procedures
- Optimization strategies for animal studies
- New approaches to safety testing including 'omics technology to study pathways of toxicity, monocyte activation test to replace the rabbit pyrogen assay and current and future performance characteristics of nonclinical safety testing
- Integration of pharmacology and safety modeling for reduced animal use; examination of a case study of the use of a transgenic mouse strain for safety testing of a monoclonal antibody

2. Symposium on Social Housing of Laboratory Animals
Co-sponsored by CAAT, US Department of Agriculture (APHIS and AWIC) and the NIH Office of Laboratory Animal Welfare (OLAW). The workshop on August 22-23, 2013 focused on problem solving to achieve social housing for social species as mandated by the new Guide for the Care and Use of Laboratory Animals. The first day centered solely on

nonhuman primates while the second day was dedicated to other species including dogs, rabbits, rodents and pigs.

3. European Refinement Initiative on Science-based Refinement
Co-sponsored by CAAT-Europe, and our sponsors Novartis and Roche, September 3-4, 2013. One session that focused on animal welfare indicators included pain assessment and endpoint refinement, welfare assessment based on adaptive capacities, and a review of euthanasia methods. The second session focused on elements of experimental design including an examination of publication bias, the quality and generalizability of animal studies, and the current efforts of CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies).

Evidence-based Toxicology Collaboration (EBTC) EUROTOX Lunch Session

This year the EUROTOX Congress in Interlaken, Switzerland, held September 1-4, featured a lunch session on EBTC on September 2. The following topics were presented:
- Evidence-based Toxicology (EBT) and the EBT Collaboration (Sebastian Hoffmann, seh consulting + services)
- EBT and Integrated Testing Strategies (Thomas Hartung, Johns Hopkins University)
- Toxicology Ontology Development supporting Evidence-based Approaches in Predictive Toxicology (Barry Hardy, Switzerland)

Joint Information Day: High Content Imaging Technology in Safety Sciences co-organized with ECOPA/ESTIV/IVTIP/SET

High Content Imaging (HCI) systems provide quantitative data from cellular assays involving automated microscopy and image analysis. These multi-parametric data sets refer to multiple endpoints and can be obtained from large numbers of cells with higher-throughput, in an observer-independent standardized way.

The information day, held October 24 in Mainz, Germany focused on the possibilities of the HCI technology for examination of damage mechanisms and toxic effects of chemicals. Probes for organelle and cell function and reporter systems for organ and systemic toxicity were presented. The discussion addressed questions on how phenotypic and signaling changes are linked to functional impairment and cell fate. Furthermore, the implementation of the HCI approach in (regulatory) safety sciences, latest technical advances and perspectives from the fields of systems biology/toxicology were important topics during this event.

Speakers from academia, industry and regulatory agencies included:
- Dr Mario Beilmann, Boehringer Ingelheim, Germany
- Dr Anthony Davies, Irish National Center for High Content Screening and Analysis (INCHSA), Ireland
- Dr Eugenio Fava, German Center for Neurodegenerative Diseases (DZNE), Germany
- Dr Roland Fleck, National Institute of Biological Standards and Control (NIBSC), UK
- Dr Manfred Kansky, F. Hoffmann-La Roche Ltd, Switzerland
- Dr Stefan Kustermann, F. Hoffmann-La Roche Ltd, Switzerland
- Prof. Marcel Leist, University of Konstanz, CAAT-Europe, Germany
- Dr Peter Mocko, European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM), Italy
- Dr Christoph Sachse, Cenix BioScience Ltd, Germany
- Dr Marianne Uteng, Novartis International AG, Switzerland
- Prof. Bob van de Water, Leiden University, The Netherlands

Upcoming events

Technical Policy Workshops on Endocrine Disruptors: a Global Overview,

November 4-5, 2013, Brussels, Belgium

On both sides of the Atlantic we see intense discussions around endocrine disruptor screening, notably the focus of the NIH Transformative Research Grant on the Human Toxome led by CAAT (http://humantoxome.com). CAAT partnered with 41 organizations to hold a workshop at Research Triangle Park in April 2013 with more than 240 scientists on first experiences from the US endocrine disruptor screening program (Juberg et al., in print). These experiences formed the basis for a two-day event in Brussels:

Day 1 (November 4, 2013): Understanding Endocrine Disruptors and available methodologies – what can we learn from experience to-date?
Location: United States Mission to the European Union
Hoover Franqui Conference Room, Boulevard du Regent 40, 1000 Brussels
Hosts: CAAT-Europe Policy Coordinator Francois Busquet and FDA Europe Deputy Director Donald Prater
Purpose and objectives: The joint venture of CAAT-Europe (University of Konstanz) and CAAT-US (Johns Hopkins Bloomberg School of Public Health) will promote transatlantic dialogue between EU & US. Some tools for performing endocrine disruptor assessments have already been validated and developed by the US Environmental Protection Agency and are being used for regulatory purposes (pesticides). In Europe, the Commission published "State of the art of the assessment of endocrine disruptors" (2002) and "The 4th implementation report of the Community Strategy for Endocrine Disruptors" (2011), which describe its strategy at the research, policy, and regulatory levels. EU and US partners will share their experience, expertise, and concerns as they both use similar test methods based on the OECD conceptual framework for endocrine disruptors.

Day 2 (November 5, 2013): Hazard/Risk assessment from the EU and the US perspectives
Location: European Parliament
Hosts: Members of the European Parliament, Vittorio Prodi and Sean Kelly (tbc)
Purpose and objectives: After DAY 1's technical meeting, DAY 2 covers the policy arena. It aims to highlight the common regulatory grounds in the perspective of Transatlantic Trade and Investment Partnership (TTIP). Topics will introduce the paradigm shift in toxicology and how Tox-21c is changing the regulatory world under TSCA (Toxic Substances Control Act) and for the EDC. Furthermore, the audience will figure out how hazard and risk assessment are perceived on both sides of the Atlantic and how they could be integrated further in TTIP.

Green Toxicology Information Day

November 22, 2013, at Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Green toxicology is the application of predictive toxicology to chemicals with the specific intent of improving their design for hazard reduction. The twelve principles of green chemistry outline a strategy to reduce hazard through molecular and process design. Reducing toxicity is at the core of green chemistry and sustainability, therefore the input of toxicologists early in the chemical enterprise is essential to inform the choices of molecular designers in selecting less hazardous design strategies. Information derived from mechanistic and computational toxicology combined forms the nexus between toxicology and green chemistry. Each group is trained to examine, understand, and describe aspects of the structure hazard relationship from a narrow perspective. This conference provides a forum for collaboration among scientists working in complementary fields to discover common ground in the quest for safer chemicals.

Public Information Day and two Workshops on Metabolomics co-sponsored by Agilent and BASF

1. Toxicometabolomics Workshop: Application of Metabolomics in Toxicology Research

November 11-12, 2013, Mt. Washington Conference Center, Baltimore, MD

This two-day workshop will start with one day of presentations from our invited metabolomics experts, followed by a second day of discussion. The workshop will bring together several metabolomics experts to share their research experiences and discuss the opportunities and challenges of the field of metabolomics in toxicological and other research. Talks focusing on research by using the metabolomics approach will be given by the invited experts to shed light on how to apply the metabolomics platform to the research. This workshop also will provide the attendees a valuable opportunity to discuss and address the issues and challenges during their research when employing metabolomics technology. The discussion session for the 2nd day of this workshop will follow the classical metabolomics workflow and provide the attendees a valuable opportunity to discuss and address the potential issues and challenges present at each step of this workflow when employing metabolomics technology in their research. Strategies used for metabolomics studies will also be discussed, which will include but not be limited to the following aspects: data acquisition; data processing; integration of metabolomics data with other 'omics' data; pathway analysis. Special focus will be dedicated to metabolomics application in toxicological studies.

2. Metabolomics Information Day: Open (Public) Meeting

November 13, 2013, Bloomberg School of Public Health, Baltimore, MD

An open (public) meeting on Metabolomics.

A mechanistic toxicology has evolved over the last decades, which is effectively relying to a large extent on methodologies which substitute or complement traditional animal tests. The biotechnology and informatics revolution of the last decades has made such technologies broadly available and useful. Metabolomics, as an emerging field of 'omics research, primarily concerns comparative analysis of the metabolites present in any biological system or any specific physiological state. It aims to characterize and identify the metabolites – the end products of cellular metabolism –, providing information on toxicological modes of action, revealing pathways of toxicity, and facilitating the identification of biomarkers.

This conference brings together scientists from academia and industry to present the current status of this technology and its applicability in toxicology:

– *Metabolomics in Cell Assay Studies:* Status and Prospects and Adverse Outcome Approaches (Thomas Hartung)
– *Metabolomics Platform at CAAT* (Liang Zhao, Johns Hopkins Bloomberg School of Public Health)
– *Metabolomics as a Tool to Assess Drug Safety* (Don Robertson, Bristol-Myers Squibb Co, Applied and Investigative Metabolomics)
– *Metabolomics as a Unique Biochemical Approach for Understanding Disease Pathogenesis* (Gary Siuzdak, The Scripps Research Institute, Center for Metabolomics and Mass Spectrometry)
– *Inclusion of a Metabolomics Approach in the Assessment of Genotoxicity of Toxicants in vitro and in vivo* (Al Fornace, Georgetown University, Lombardi Comprehensive Cancer Center)
– *Quality Aspects of Metabolomics Studies* (Mounir Bouhifd, Johns Hopkins Bloomberg School of Public Health)
– *Using the Serum Exposome to Discover Causes of Disease* (Anthony Macherone, Agilent Technologies, Inc. and Visiting Scientist, Johns Hopkins School of Medicine)
– *Discovering Biomarkers of Human Disease and Development Using Stem Cells and Metabolomics* (Paul West, Stemina Biomarker Discovery, Inc.)
– *Application of Metabolomics in Preclinical and Industrial Toxicology – MetaMapTox* (Hennicke Kamp, BASF SE, Experimental Toxicology and Ecology)

3. Workshop on Quality Assurance of Metabolomics

November 14-15, 2013, Bloomberg School of Public Health, Baltimore, MD

The goal for this workshop is to consider the challenges associated with metabolomics as an emerging science in toxicology and to identify what key issues must be addressed in order to establish and implement quality assurance procedures in metabolomics based toxicology. We anticipate discussing quality control tools to help ensure sound science and reproducible research. The consortium is also expected to discuss guidelines for metabolomics data generation, standardization, and analysis. NIH Research Project "Human Toxome" participants, together with invited experts from academia, industry, and regulatory agencies will share their experience and discuss the following topics:

- Quality assurance in metabolomics for modern toxicology: a hassle or a need?
- Components of reproducibility in metabolomics studies
- Platforms, acquisition, processing
- Experimental design and reporting standards
- Resources (databases), integration (with other 'omics), transferability
- Elements of a quality system in toxicometabolomics
- Value and use of information in decision-making

In Vitro Medical Device Testing Symposium

December 10-11, 2013, Johns Hopkins Mt. Washington Conference Center, Baltimore, MD

Platinum Sponsor: NAMSA; Supporters: Cook Medical and Medtronic Inc.

This symposium, hosted by CAAT, will examine how the National Academy of Sciences' *Toxicity Testing in the 21st Century: A Vision and a Strategy* can be applied to medical devices. The program will examine current requirements and testing approaches, followed by an examination of *in vitro* assays useful in medical device testing.

Non-animal models of epithelial barriers (intestine, skin, lung) in research and industrial applications

February 19-21, 2014, Saarbrücken, Germany

The effect of pharmaceuticals, chemicals, cosmetics, and food ingredients is highly dependent on their distribution at the cellular, organ, and whole system level. Some compounds are able to cross biobarriers by diffusion or active transport, e.g., therapeutics and nutrition. The active or passive transport of other compounds across barriers may pose a threat, e.g., bioresistant nanomaterials may access the systemic circulation and cause undesired effects. In addition, biobarriers themselves may be targets for therapeutic intervention or may be exposed to toxic and other adverse effects. The *in vitro*, *ex vivo*, and *in silico* biobarrier models will be discussed in this workshop with regard to their functionality and fitness-for-purpose from academic, industrial, and regulatory points of view.

Fourth International Conference on Alternatives for Developmental Neurotoxicity Testing (DNT): Advancing the Science of Developmental Neurotoxicity Testing for Better Safety Evaluation

May 12-14, 2014, Philadelphia, PA

Developmental neurotoxicity from chemical exposures is a growing concern. The developing human nervous system is susceptible to pharmaceuticals and environmental contaminants, and exposure during development is known to cause lasting neurological deficits. This conference will bring together diverse stakeholders from around the globe, including research scientists, regulators, industry representatives, academics, and pediatricians.

You are invited to submit an abstract on the following DNT topics:

- Development and use of alternative testing methods and strategies
- Automation of test methods
- Models of chemical-induced neurological deficits
- The impact of international legislation on chemical testing and data interpretation
- Toxicity pathways: Linking molecular events to adversity (AOP and PoT)
- Predictive molecular and cellular biomarkers of DNT
- Modeling gene/environment interactions that impact neurodevelopment
- Epigenetic changes and neural development

Communication Program

Our program continues to achieve high visibility. A one-day visit to NIEHS found very nice coverage in their journal Environmental Factor:

"A Plan for Revolutionizing Toxicology Testing for the 21st Century"

"The difficulty lies not so much in developing new ideas as in escaping from old ones." – John Maynard Keynes

While this quote concluded the July 17 NIEHS Office of the Director seminar by grantee Thomas Hartung, M.D., Ph.D., it expressed the overarching theme of his presentation, "The Human Toxome, Evidence-Based Toxicology, and Integrated Testing Strategies – Additions to the Toolbox of 21st Century Toxicology?" The talk was hosted by NIEHS and NTP Director Linda Birnbaum, Ph.D., who described Hartung as one of the leaders in the field of predictive toxicology.

Hartung discussed a three-pronged approach for the future of toxicology testing, utilizing organotypic cultures, pathways of toxicity (PoT), and integrated testing strategies (ITS). This 21st century toxicology toolkit seeks to revolutionize the field, opening up avenues for biomarker identification, the identification of non-hazardous chemicals, and greener design through predictive toxicology…"

Full article (Environmental Factor, August 2013) NIEHS available at: http://www.niehs.nih.gov/news/newsletter/2013/8/science-plan/index.htm

Other examples include:

BBC Article: Will We Ever ... Eliminate Animal Experimentation? Features Thomas Hartung. Available at: http://www.bbc.com/future/story/20130609-will-we-ever-end-animal-testing

Chemical Watch Article by Emma Davies: *Giving screening the green light*

By working with toxicologists while they're designing new compounds, chemists can avoid problems further down the chain… In December 2012, the EPA in New England teamed up with the Johns Hopkins Centre for Alternative Animal Testing (CAAT) to run a toxicology and sustainable molecular design conference and a green toxicology seminar is scheduled for November 2013.

"Green toxicology is similar to the idea in the pharmaceutical industry of frontloading toxicity assessments – fail early, fail cheaply," explains CAAT director Thomas Hartung.

"While expensive and long animal tests are of little help, in vitro and in silico approaches promise to do the trick." At such an early stage in a chemical's development, false negative and false positive results are considered acceptable. "Unlike their regulatory use, the applications do not need the ultimate proof of predicting each and every possible adverse effect as the regulatory evaluation is coming later anyway," says Hartung. Both groups benefit, he adds. "Chemists don't like to see substances die late on and toxicologists have found new customers who don't require 10 years of validation before they use their tools."

Recent publications by CAAT/ CAAT-Europe Faculty

Hogberg, H. T., Bressler, J., Christian, K. M., et al. (2013). Toward a 3D model of human brain development for studying gene/environment interactions. *Stem Cell Res Ther 4, Suppl 1*. doi:10.1186/scrtX

Juberg, D. R., Borghoff, S. J., Becker, R. A., et al. (2013). Lessons Learned, Challenges, and Opportunities: The U.S. Endocrine Disruptor Screening Program. *ALTEX*, Oct 10. Epub ahead of print. http://www.altex.ch/resources/WR_Juberg_epub.pdf

Kleensang, A., Maertens, A., Rosenberg, M., et al. (in print). Pathways of Toxicity. *ALTEX*, Epub ahead of print. http://www.altex.ch/resources/WR_Kleensang_epub.pdf

Krause, K. H., van Thriel, C., De Sousa, P. A., et al. (2013). Monocrotophos in Gandaman village: India school lunch deaths and need for improved toxicity testing. *Arch Toxicol*, Aug 13. Epub ahead of print. http://link.springer.com/article/10.1007%2Fs00204-013-1113-6#page-1

Krug, A. K., Balmer, N. V., Matt, F., et al. (2013). Evaluation of a human neurite growth assay as specific screen for developmental neurotoxicants. *Arch Toxicol*, May 14. Epub ahead of print. http://link.springer.com/article/10.1007%2Fs00204-013-1072-y#page-1

EUSAAT

European Society for Alternatives to Animal Testing

News from EUSAAT

EUSAAT, the European Society for Alternatives to Animal Testing, the European 3Rs Society, welcomes the opportunity to present recent activities in the EUSAAT news corner of our official journal ALTEX. In this issue, our commentary summarizes some highlights from the Linz 2013 – EUSAAT 2013 conference and reports on the election of the new EUSAAT Board.

Conference Linz 2013 – EUSAAT 2013

From September 15 until 18, 2013 EUSAAT held its well-established Conference Linz 2013 – EUSAAT 2013, i.e., the 18th European Congress on Alternatives to Animal Testing – Linz 2013 and 15th Annual Congress of EUSAAT. As proven and tested, EUSAAT was grateful to once again have the opportunity to convene at the Johannes Kepler University in Linz, Austria. More than 200 participants from all over Europe, as well as from North America, Russia, Japan, and Sri Lanka joined EUSAAT for four days of state-of-the-art lectures on alternatives to animal experiments in accordance with the 3Rs principle.

Conference Topics included the implementation of European Union (EU) Directive 2010/63/EU on the protection of animals used for scientific purposes and the ethical implications of animal experimentation in accordance with the provisions of this new EU Directive, consequences of the 2013 EU marketing ban for cosmetic ingredients tested on animals, alternative methods for specific endpoints of toxicity testing, latest research on *in vitro* 3D models and "human-on-a-chip" models, and the challenge of implementing alternatives into basic research. Extensive poster sessions provided ample opportunity for experienced and young scientists to engage in lively discussions, to exchange information on the application of alternative methods in accordance with the 3Rs principle, and thereby possibly also found the basis for new collaborations.

One of the highlights of the more than 40 lectures underlining the close collaboration of EUSAAT with international scientific institutions worldwide was the presentation by Dr Hajime Kojima from the Japanese National Institute of Health Sciences in Tokyo who reported on the Japanese project "*ARCH-Tox*" *for the future chemicals management policy: research and development of in vitro and in vivo assays for internationally leading hazard assessment and test methods* (presentation abstract in *ALTEX Proceedings 2(2),* 56).

Susanna Louhimies, senior policy officer of the General Directorate Environment of the European Commission in Brussels, responsible for Directive 2010/63/EU, outlined recent work in implementing its provisions, and specifically gave an *Overview of the Work of Commission Expert Working Groups on an EU Framework for Education and Training and on Project Evaluation* (see *ALTEX Proceedings 2(2)*, 72). From an EU Member State perspective, this EU activity report was supplemented by the presentation from Dr Katharina Kluge, German Federal Ministry of Food, Agriculture and Consumer Protection, Bonn, who reported on the challenges of *Implementing Directive 2010/63/EU into German Law* (*ALTEX Proceedings 2(2)*, 54).

Professor Dr Horst Spielmann, Free University of Berlin, the former and re-elected President of EUSAAT, held the Willi Halle Memorial Lecture *Today, Willi Halle would Endorse the Concept "Toxicity Testing in the 21st Century"* (*ALTEX Proceedings 2(2)*, 116) in honour of EUSAAT's honorary member Willi Halle who, despite the unsupportive political system of the former German Democratic Republic, collected *in vivo* acute toxicity data and *in vitro* cytotoxicity data for 347 chemicals with great personal dedication. When the German-German frontier finally opened in 1998, he immediately contacted ZEBET, the German Centre for Documentation and Evaluation of Alternatives to Animal Experiments (*Zentralstelle für die Erfassung und Bewertung von Ersatz- und Ergänzungsmethoden zum Tierversuch*) at the Federal Institute for Risk Assessment (BfR; *Bundesinstitut für Risikobewertung*) in Berlin. ZEBET supported him in publishing this unprecedented collection of data in the form

of the Register of Cytotoxicity Toxicity Testing in Cell Cultures to Predict Acute Toxicity (LD_{50}) and to Reduce Testing in Animals (*Altern Lab Anim 31*, 89-198). Sadly, Willi Halle passed away on May 26, 2013 at the age of 84.

Impressively documenting the challenges of newly introducing the 3Rs principle and humane experimental techniques into established research structures, Dr Mangala Gunatilake, University of Colombo, Sri Lanka, highlighted the *Steps Taken to Implement 3Rs Concept in Research Using Animals in Sri Lanka* (*ALTEX Proceedings 2(2)*, 34).

As a part of the conference, ESNATS, the collaborative research project Embryonic Stem cell-based Novel Alternative Testing Strategies, funded under the EU 7th Research Framework Programme, held a one-day session on the *Use of Human Embryonic Stem Cells for Novel Toxicity Testing Approaches*.

Finally, documenting EUSAAT's special dedication in supporting the education of young scientists, a special "Training course on non-animal test methods for topical toxicity testing" was held as satellite meeting on September 18 and 19, 2013. Fifteen young scientists from five European and two South American countries made use of this unique opportunity to gain 'hands-on' experience in using cell techniques for skin penetration studies, reconstructed tissue models for skin irritation and corrosion testing, as well as the HET-CAM assay for eye irritation testing. Enthusiastic feedback at the end of the training course underlined the importance to continue such training courses alongside future Linz – EUSAAT conferences.

EUSAAT Board elections

During the Linz 2013 – EUSAAT 2013 conference, the EUSAAT Annual General Assembly took place, which this year, included the elections of the new Board for the upcoming four-year term. Professor Dr Horst Spielmann, Free University of Berlin, was re-elected as President of the Society. Dr Eleonore Haltner-Ukomadu, founder and CEO of Across Barriers GmbH, Saarbrücken, Germany, and Professor Dr Ellen Fritsche of the IUF – Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany, were elected as Vice Presidents. Dr Ursula G. Sauer, freelance Scientific Consultancy – Animal Welfare, Neubiberg, Germany, was elected as Secretary General. Further Board Members, completing the round, are Dr Dr Stefanie Schindler, Animalfree Research, Bern, Switzerland and President of the Society ALTEX Edition, and Dr Candida Nastrucci, President and founder of TheAlternatives.eu and lecturer and organizer of courses on non-animal alternatives at the University of Tor Vergata, Rome, Italy.

The new Board, which took up its tasks and duties with immediate notice, is dedicated to combining efforts and commitments to join forces in promoting the 3Rs principle and alternatives to animal testing. In this context, the Secretary General is currently preparing a Task Force which will work via e-mail correspondence. As agreed upon at the AGA 2012, all interested members of EUSAAT are invited to join the Task Force to discuss the goals of EUSAAT with the aim of updating them, as necessary, by integrating approved and established areas of work of our European 3Rs society with new ideas and motivations.

Special thanks and acknowledgements for previous Board members and poster awards

During the social evening, the congress participants joined the new Board in thanking the previous Board members Professor Dr Walter Pfaller, PD Dr Franz P. Gruber, and Professor Dr Dr Thomas Hartung, former Vice Presidents of EUSAAT, and Helmut Appl MSc, former Secretary General, for their year-long continued dedication and hard work in supporting the society and the continuity of the Linz Conferences. Helmut Appl also holds the congress office for the Linz 2013 - EUSAAT 2013 conference.

At the social evening, the two EUSAAT poster awards were presented to:

Lilian J. Löwenau, S. Wattanapitayakul, J. M. Brandner, G. Weindl, and M. Schaefer-Korting from the Institute for Pharmacy of the Free University, Berlin, in cooperation with the Department of Pharmacology of the Srinakharinwirot University, Bangkok, Thailand, and the University Clinic Hamburg Eppendorf, Germany, for their poster *Human epidermis reconstructed from UVB-irradiated keratinocytes mimics premature ageing in human skin* (*ALTEX Proceedings 2(2)*, 73); and to Katy Taylor from the British Union Against Vivisection/European Coalition to End Animal Experiments, London, UK, for her poster *A 'low toxicity profile' can waive the 90-day repeated dose test for REACH* (*ALTEX Proceedings 2(2)*, 122).

Additionally, the Poster Award of the Austrian Animal Welfare Foundation Four Paws – *Vier Pfoten* was presented to Tobias Hasenberg, E. M. Materne, C. Frädrich, U. Süßbier, R. Horland, S. Hoffmann, S. Brincker, A. Lorenz, M. Busek, F. Sonntag, R. Lauster, and U. Marx from the Technical University, Berlin, and the Fraunhofer Institute IWS (*Institut für Werkstoff und Strahltechnik*) for the poster *Dynamic culture of human liver equivalents inside a micro-bioreactor for long-term substance testing* (*ALTEX Proceedings 2(2)*, 36).

Upcoming events

As has been common practice for many years, the annual Linz conferences are not held during years in which a World Congress on Alternatives takes place. Therefore, since the 9th World Congress on Alternatives and Animal Use in the Life Sciences will be held from August 24-28, 2014 in Prague, Czech Republic, addressing the topic *Humane Science in the 21st Century* (http://www.wc9prague.org), next year there will be no Linz conference, and the EUSAAT AGA will be convened in Prague.

Ursula G. Sauer
Secretary General of EUSAAT
the European 3Rs Society
on behalf of the Board

News from NICEATM and ICCVAM

Advisory Committee considers new vision and direction for ICCVAM

The ongoing changes to NICEATM and ICCVAM were a major focus of this year's meeting of the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), which met on September 24. SACATM is composed of ICCVAM stakeholders from various industry groups, academia, and animal welfare organizations, and meets annually to advise NICEATM and ICCVAM on their activities.

Earlier this year, National Institute of Environmental Health Sciences (NIEHS) and National Toxicology Program (NTP) Director Linda Birnbaum, PhD, called for significant changes to the focus and priorities of both NICEATM and ICCVAM. ICCVAM has responded by developing a proposal for a new strategic direction, which is outlined in a document titled "A New Vision and Direction for ICCVAM." The proposal was described to SACATM in presentations by acting ICCVAM Co-Chair Anna Lowit, PhD, of the U.S. Environmental Protection Agency and acting NICEATM Director Warren Casey, PhD.

"A New Vision and Direction for ICCVAM" describes initial steps in response to the calls to reinvigorate ICCVAM. Specifically, the document discusses: 1) ICCVAM priority setting and areas of scientific focus for immediate resource investment; 2) plans to improve communications with stakeholders and the public; and 3) exploration of new paradigms for the validation and utilization of alternative toxicological methods. A key goal of the realignment of NICEATM and ICCVAM is to have the ICCVAM member agencies take a more active role in priority setting and operations so that ICCVAM can devote the most effort to those projects that are the most interesting and useful to the member agencies.

In the proposal, ICCVAM identifies several projects where advances in science have made putting alternative methods into regulatory use likely in the near term. These areas include non-animal methods for testing vaccines that protect pets and livestock against the disease leptospirosis, testing to identify substances that could be poisonous when ingested or absorbed through the skin, and testing to identify substances that could cause allergic contact dermatitis.

The proposal and descriptions of associated activities were warmly received by both SACATM members and meeting attendees. "ICCVAM's new vision, validation strategies, and project pipeline are a welcome revision that, if successful, will not only bring ICCVAM in line with current scientific advances, but will reinstate ICCVAM's role as a facilitator in the development and regulatory use of alternative methods," commented Catherine Willett, PhD, of the Humane Society of the United States.

In addition to discussing the new ICCVAM vision and procedures, SACATM members also received updates about current NICEATM projects related to skin sensitization, a report from the U.S. government's interagency Tox21 high throughput screening program, and summaries of last year's ICCVAM-sponsored workshops on alternatives to animal testing for *Leptospira* and pertussis vaccines.

Information about the SACATM meeting, including "A New Vision and Direction for ICCVAM" and all presentations, is available on the NTP website at: http://ntp.niehs.nih.gov/go/8202

NICEATM collaborates with industry scientists to develop statistical approach to identify skin sensitizers

Traditional testing methods to identify skin sensitizers use animals, but regulatory requirements and concerns about testing efficiency and animal welfare are driving efforts to replace traditional testing methods with non-animal methods. NICEATM is collaborating with NTP statisticians and scientists at Procter and Gamble in Brussels, Belgium, to create an integrated test strategy to identify potential skin sensitizers using non-animal

test methods. The integrated test strategy is described in a short communication that is currently being prepared for publication.

In practice, it usually takes several non-animal tests to provide the same level of information as a single animal test. An integrated test strategy developed by Procter and Gamble scientists provides an approach for analyzing information from nonanimal tests and other information about a test substance, such as chemical structure and solubility. The analysis considers available relevant information about a substance and produces a numerical probability that the substance is a sensitizer, and how strong or weak it might be. This probability could potentially be used to make decisions about whether substances require hazard labeling without requiring animal testing.

The software used by Procter and Gamble for these analyses is proprietary, so the goal of the NICEATM collaboration was to develop similar tools using the publically available R software package to make the integrated testing strategy approach more widely usable. More information about the integrated test strategy is available on the NTP website at http://ntp.niehs.nih.gov/go/its. Those wishing to know more about the integrated test strategy tool may view frequently asked questions, register for a user community email list, and download files from this page.

Acting NICEATM Director participates in International Meeting in Seoul

Acting NICEATM Director Casey traveled with other National Toxicology Program scientists to the 2013 International Congress of Toxicology meeting in Seoul, South Korea, which took place June 30 through July 4. The trip provided the U.S. delegation an opportunity to present updates on current projects and interact with international colleagues.

A key interaction was Casey's presentation on NICEATM activities at a July 3 coordination meeting of the International Cooperation on Alternative Test Methods (ICATM). ICATM is an international partnership that promotes the advancement of replacement, reduction, and refinement alternatives for animal testing.

The ICATM coordination meeting included updates from Europe, Japan, Korea, and the U.S. on their current test method evaluation and validation activities. Casey discussed ongoing changes at NICEATM and ICCVAM, and provided an update on NICEATM activities supporting Tox21 and NICEATM collaborations to develop new models to identify skin sensitizers.

Currently, finding replacements for animal tests to identify potential skin sensitizers is a major focus of ICATM member organizations, and most of the discussion at the July ICATM meeting focused on this topic. However, member organization representatives also provided updates on studies of alternative test methods to identify potential eye irritants, carcinogens, and endocrine active substances.

ICATM currently includes member organizations from the European Union, U.S., Japan, Canada, and South Korea. The government of Brazil recently established the Brazilian Center for Validation of Alternative Methods (BraCVAM). BraCVAM will begin participating in ICATM coordination meetings as an observer this fall.

ICATM coordination meetings take place several times a year and provide an opportunity for the five member organizations to discuss activities in the major areas of cooperation. Regular interactions allow the ICATM partners to develop good communications and working relationships, which support collaborations on test method development.

Institute for In Vitro Sciences
Advancing Science & Animal Welfare Together

IIVS News & Views

IIVS, HSI, HSUS, and HTPC sign a Memorandum of Understanding

To further the activities of its International Outreach Program, IIVS signed a Memorandum of Understanding (MOU) with The Humane Society of the United States (HSUS), Humane Society International (HSI), and the Human Toxicology Project Consortium (HTPC). HSI and HSUS are organizations advocating for better laws to protect animals through education and hands-on training, among many other activities geared toward seeking a humane and sustainable world for animals and humans. The HTPC mission is to serve as a catalyst for the prompt, global, and coordinated implementation of pathway-based toxicology, which will better safeguard human health and hasten the replacement of animal use in toxicology. The MOU is the product of a mutual desire by HSI, HSUS, HTPC, and IIVS to collaborate toward toxicological science/policy progress in China through education and hands-on training in the use and interpretation of OECD-accepted *in vitro* test guideline methods and dialogue with Chinese authorities. An example of the work supported by this effort can be found in the section below.

Chinese Society of Dermatology Meeting

In June 2013, IIVS staff attended the 19th Annual Meeting of the Chinese Society of Dermatology in Chengdu, China (Sichuan province). A presentation by Dr Brian Jones, the former Director of Education and Outreach at IIVS, gave an update on the regulatory status of non-animal methods used in safety assessment, examples of how cosmetic and personal care companies utilize non-animal tests, and a description of the standards being established around the world to eliminate animal testing for the evaluation of cosmetics.

Over 9,000 dermatologists attend this conference annually including representatives from domestic and international cosmetic companies as well as those dermatologists who are selected by the CFDA as expert reviewers of functional cosmetics (skin lightening, SPF, etc.). Having a greater knowledge of non-animal test methods and how they are used within the industry will help facilitate their implementation in safety testing programs and acceptance during safety reviews.

The IIVS presentation was given during the Cosmetic Dermatology session chaired by Dr Lai Wei, Chairman and Director – Department of Dermatology of the 3rd Affiliated Hospital of Sun Yat-Sen University, Guangzhou and Dr Liu Wei, Head of Dermatology, General Hospital of Air Force, Vice-Chair National Standard Committee of Cosmetics, Beijing. The session was highly attended with an estimated 300 people. Many questions were posed by cosmetic company representatives from both domestic Chinese and international companies with China-branch offices. During the conference, Dr Quanshun Zhang, IIVS' new Manager of International Education and Outreach, was invited by Gala Group, one of the largest Chinese cosmetic companies, to give a further presentation about the application of *in vitro* methods for testing cosmetic products and ingredients at the Skin Biology Symposium in October, 2013.

Attendance at both of these meetings is part of IIVS' International Outreach Program (http://bit.ly/19wQ2XY) and was generously supported by the Humane Society of the United States (HSUS), Humane Society International (HSI), and the Human Toxicology Project Consortium (HTPC).

Training and mentoring Quality Assurance personnel and study directors

IIVS continuously strives to interact with its partners to advance the field of *in vitro* toxicology and is committed to being a resource for the benefit of the scientific community. We are well known for educating via our hands-on and lecture based training sessions and targeted technical workshops, but our actions to promote high quality science extend beyond those efforts.

The Society for Quality Assurance (SQA) is an association of over 2,300 QA professionals in more than 30 countries who are dedicated to implementing Good Clinical Practices (GCPs), Good Laboratory Practices (GLPs), and Good Manufacturing Practices (GMPs) in industry, government, academia, and consulting. SQA provides valuable training and networking opportunities for its members. Amanda Ulrey, Head of Quality Assurance at IIVS, was elected by her SQA peers to serve as a member of the Education Committee. In this role, she is responsible for reviewing and discussing training opportunities for SQA members. The Education Committee identifies the professional development needs of the society membership and coordinates training and professional enhancement opportunities through workshops, lectures, symposia, and online presentations. Ms. Ulrey works to share the IIVS culture of quality philosophy with the SQA membership.

Mentoring is an integral part of training and IIVS is working towards becoming more involved in mentoring programs for quality assurance professionals. As an example, Ms. Ulrey currently serves as the chair of the SQA Mentor Committee. This committee administers the Mentoring Program by evaluating mentor/mentee/peer partner applications and facilitating professional relationships. In addition to serving on the committee, Ms. Ulrey has been a mentor to other quality assurance professionals throughout the United States, Korea and Nigeria, helping them expand their knowledge of regulatory compliance and develop the skills necessary to be a successful quality auditor. Each member of the IIVS QAU staff has participated in mentoring relationships and discussions within the Good Laboratory Practices (GLP) and Scientific Archiving Specialty Sections, and the Computer Validation Initiative Committee (CVIC) of SQA. For more information on the IIVS Quality Assurance Program, please visit our website (http://www.iivs.org).

In addition to educating quality assurance professionals, IIVS staff also strive to promote educational opportunities for other scientific professionals, such as study directors. Dr Gertrude-Emilia Costin (IIVS Study Director) and Mr. Hans Raabe (Vice President and Director of Laboratory Services) have authored a chapter entitled "*In Vitro* Toxicology Models" as part of a book designed to educate new and potential study directors in the workings of a nonclinical safety testing environment. The book, titled *The Study Director in Nonclinical Studies for Drugs, Chemicals, Pesticides and Devices* (editors William J. Brock, Barbara Mounho, Lijie Fu), is scheduled for release in early 2014, and is published by John Wiley and Sons, Inc.

Congratulations to the 2013 ARDF Grant recipients

IIVS has coordinated the grant review process for Alternatives Research and Development Foundation (ARDF) and has provided input into submissions for the past several years. We would like to congratulate each of this year's five recipients. The 2013 Alternatives Research Grant Program has awarded $ 200,000 to scientists developing alternative methods in a variety of areas of medical research, testing, and education. To view the recipients, please visit the ARDF website at: http://www.ardfonline.org