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ESTIV

The European Society of Toxicology *In Vitro*

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Editorial

Dear ESTIV members,

Here is the new ESTIV newsletter including an update on *in vitro* toxicology, information on activities undertaken in the last six months and those planned for the near future.

Heartiest congratulations to CAAT-Europe for 2014 LUSH Prize, to Dr. Martin Stephens for Russel and Burch Award and to Professor Marcel Leist who received the SOT Enhancement of Animal Welfare Award.

This issue includes many events on interesting and current topics such as the training course organized by the European Society of Toxicology *In Vitro* (ESTIV), National Institute of Public Health (SZÚ) and the European Society for Alternatives to Animal Testing (EUSAAT), the workshop organized by the SLIM project consortium at the 9th World Congress held in Prague and the LIFE-EDESIA organized in Milan, Italy. You will also find information on the initiative "MEP—3Rs scientist pairing scheme" and a new glossary, first published in ALTEX and now available on Altweb.

I would like to thank all members for their contribution and all others who have collaborated on this issue. Hope you also find this information of interest,
best wishes to all

Francesca Caloni

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Message from the President

Dear members,

The last months have been marked by a series of events that you will find reported in the present newsletters. In particular ESTIV has organized two successful training courses dedicated to the practical and applied aspects of *in vitro* toxicology in Czech Republic and in Portugal respectively. Both training courses were fully booked in advance, and counted with participants from industry, academia and regulatory bodies coming from over 20 European and outreaching countries such as Australia, Brazil, China, Russia and US. The ESTIV Board will continue its efforts to organize similar training activities in future, in addition to the regular scientific workshops and congresses, in order to continue to promote *in vitro* and *in silico* toxicology uses and applications and strengthen the scientific network in our field.

We are also pleased to announce that the next ESTIV Congress will take place in Juan-les-Pins, France in October 2016 kindly hosted by the French Society of Toxicology. It will be a great occasion to address the latest scientific advances in the areas of *in vitro* and *in silico* toxicology, as well as how such tools are currently being integrated and used for risk and hazard assessment purposes considering the specific needs in the various sectors such as biocides, cosmetics, environmental hazards, food, household products, pharmaceuticals and tobacco.
I take the occasion to welcome Dr. Philippe

Bourrinet who will be responsible for the ESTIV 2016 Congress organization at the ESTIV Board.

Finally, I am pleased to announce that ESTIV has become, since September 2014, an affiliated society to EUROTOX. As an ESTIV member you can now benefit amongst others, from a free EUROTOX membership and a reduced fee for attending the EUROTOX congresses. I hope you will enjoy these advantages!

Wishing you a year with many professional successes!

Chantra Eskes
ESTIV President

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WC9 Practical Training Course on Alternative Methods: Skin and Eye *In Vitro* Toxicity

28–29 August, 2014, Prague, Czech Republic

A training course, with the focus on *in vitro* skin and eye toxicity testing, was organized by the European Society of Toxicology *In Vitro* (ESTIV), National Institute of Public Health (SZÚ) and the European Society for Alternatives to Animal Testing (EUSAAT) on August 28-29, 2014 as a satellite meeting of the 9th World Congress on Alternatives and Animal Use in the Life Sciences (WC9)
Lectures on alternative methods for skin and eye irritation and corrosion testing were presented on Thursday August 28th by **Dr. Chantra Eskes** (ESTIV/SeCAM, Switzerland), **Dr. Helena Kandarova** (MatTek IVLSL/SETOX, Slovakia), **Dr. Kristína Kejlvá** (SZÚ/Czech Republic) and **Dr. Hans Raabe** (IIVS, USA) after the conclusion of the World Congress meeting.
Hands-on laboratory activities, composed of 3 training blocks (Reconstructed human skin models – OECD TG 439, Corrositex assay – OECD TG 435 and HET-CAM assay), took place the following day.

The training was hosted at the Czech National Institute of Public Health campus and was dedicated to students and scientists at the beginning of their career in *in vitro* toxicology. The course was fully booked in advance and hosted attendees from academia , regulatory bodies and industry coming from 13 European and outreaching countries such as Australia, Brazil, China and Russia.

From the discussions as well as from the training evaluation forms received after the completion of the course, the organizers conclude that the training course met the expectation of the participants both scientifically as organizationally. Some of the comments received:

- *"I liked to try and learn new methods, even if I knew some theoretical background about them already. Seeing it in person and performing it with my hands is different".*
- *" The duration of the workshop is just nice. It is not too hectic and more information could be absorbed in this short and fruitful workshop. The interaction between trainers and trainees during the practical session is awesome."*

The photos show the interactive atmosphere of the practical session on HET-CAM assay and the almost complete group of the participants and trainers.

More information about the program, organizers and supporters can be obtained at:

http://www.wc9prague.org/satellite-meetings/course-on-alternative-methods/

Dr. Helena Kandarova
ESTIV Communications

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ESTIV-APTox Applied *In Vitro* Toxicology Course
25-29 January 2015, Cascais, Portugal

From 25 to 29 January 2015, ESTIV, together with the Portuguese Toxicology Association (AP Tox), organized for the first time the "Applied *in vitro* toxicology course", held in Cascais-Portugal. The program was focused on 3 domains, namely regulatory, industrial and investigative *in vitro* toxicology. The theoretical part of the course consisted of 18 state-of-the-art presentations covered by 8 lecturers, including Paula Alves (Animal Cell Technology Laboratory, Oeiras-Portugal), Bas Blaauboer (Utrecht University-The Netherlands), Sandra Coecke (JRC-Italy), Chantra Eskes (SeCAM-Switzerland), Paul Jennings (Innsbruck Medical University-Austria), Nathalie Lambrechts (Flemish Institute for Technological Research-Belgium), Jochem Louisse (Wageningen University-The Netherlands) and Mathieu Vinken (Vrije Universiteit Brussel-Belgium). This was complemented by a practical group exercise, in which the participants were asked to search and critically evaluate *in vitro* toxicity testing data of specific compounds. The presentation of the outcome of this group exercise, followed by a thorough discussion with the lecturers, served as the course exam. The course program also contained a number of social events, including social diners and a sightseeing visit to Lisbon, that favoured interaction and networking amongst participants and lecturers.

The course was attended by 20 participants from academia, industry and regulatory agencies coming from 15 different countries. Among them, Celia Fernández-Blanco (Spain), Sofia Batista Leite (Belgium) and Sebastian Prill (Germany), received an ESTIV grant, which included a full waiver of the course fee. The quality of the presentations of the participants as well as the level of the subsequent discussions at the end of the course was very high. All attendees received a course certificate. The course evaluation survey, that was anonymously completed, rated the overall course program and organization with the highest score, very good, and all lectures as being good to very good. Some of the comments received were:

- "*Nice speakers, well organized, good program = Good Job!*"
- "*Very high level.*"
- "*Very nice selection of topics/lecturers and logic sequence*."

The recipients of the ESTIV bursary for this course (from left to right: Sofia Batista Leite, Sebastian Prill, Celia Fernández-Blanco).

ESTIV intends to organize this course on a 2-yearly basis alternating with its conferences. The next course will probably take place in Luxemburg in January 2017 as a joint activity with The Belgian Society of Toxicology and Ecotoxicology (BelTox). Furthermore, negotiations are currently ongoing to get the ESTIV course officially recognized by EUROTOX as a module of the program to acquire the European Registered Toxicologist (ERT) accreditation. This will add significant value and will increase the visibility of the course, in turn further promoting the use of *in*

vitro toxicology methods and 3R-alternatives in general in Europe and beyond.

Mathieu Vinken, Elsa Casimiro & Chantra Eskes

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Increasing (Corporate) Responsibility to use of Animals in R&D: Establishing criteria for an independent 3Rs index?

28 August 2014, Prague at the 9TH World Congress on Alternatives Animal Use in the Life Sciences

The SLIM project consortium organized a very successful workshop due to the participation of more than sixty people from industry, academia and regulatory bodies. At the end of the presentations, accompanied by a lively discussion we concluded that the idea to develop a "3Rs index" as a motor for corporate responsibility of industry for the use of animals and the implementation of 3R-methods, was supported by the participants.

The 3Rs index is proposed as a benchmarking tool that could rank industry and other organizations, such as research institutes that use experimental animals. Benchmarking of companies is not a novel tool. One example of an existing index is the Access to Medicines Index (ATMI; www.accesstomedicineindex.org). Peter Kustermans, affiliated to the ATMI Foundation, presented an overview on the multi-stakeholder ATMI approach.

Gill Fleetwood (Glaxo Smith Kline) shared her views on the feasibility of a 3R index, based on GSK's experience with ATMI. The success of a 3R index will be highly dependent on the willingness of a company to integrate policies on Animal welfare in the company daily business. The same applies for the ATMI or any Index; the company must "live" the index. GSK reported their positive experience with the ATMI: "*ATMI is an opportunity to share our strategy, it's one way to assess how well we're doing rather than a driver; it can show what you are doing; companies are asked to give input on the methodology; non-disclosure agreement is in place; and it provides examples of good practices*."

Finally, Cyrille Krul gave an overview of the 'SLIM' project. The idea to investigate the feasibility of a 3R index originated from a previous workshop on communication and Corporate Social Responsibility programs. The best way to stimulate companies to address Animal Welfare and 3R is to identify individual stakeholders, reward front runners and stimulate initiatives. To achieve this a 3R-index can facilitate and accelerate this process.

The report of the workshop can be downloaded at: www.innovativetesting.nl/slim or for further information contact: cyrille.krul@hu.nl

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The LIFE-EDESIA project: applying functional biomarkers to support the substitution principle of endocrine disrupting chemicals

December 2014, Milan, Italy

Within the frame of the REACH Regulation (2006/1907/EC), Endocrine Disrupting Chemicals (EDCs) have an *equivalent level of concerns* to Substances of Very High Concern (SVHC; REACH art. 57). The substitution principle is a REACH building block that, in the EDC case, deals with the identification of "equivalent" chemicals with a lower, or absent, endocrine disrupting effect(s).

Dr Lorenzetti and Dr Mantovani Life EDESIA Chairs

To support the substitution principle, the LIFE-EDESIA project (LIFE12 ENV/IT/000633, coordinated by the Istituto Superiore di Sanità - ISS, Rome, www.iss.it/life) is developing an integrated *in silico-in vitro* approach to demonstrate that such alternatives can be screened through non animal testing strategies and by the application in EDC

toxicology of *in vitro* assays exploiting cell specific, functional biomarkers, already in use in human medicine (*e.g.,* Prostate-Specific Antigen – PSA). Alternatives to the LIFE-EDESIA targeted chemicals (phthalates, bisphenols and parabens) will be screened by a set of *in silico* methods (from chemico-physical and nuclear receptor binding properties to molecular docking and QSAR) and then evaluated *in vitro* for their endocrine disrupting effects in three different cell types representative of endocrine-targeted human cells (trophoblasts, fetal hepatocytes and prostate epithelial cells). Alternatives will be proven as "equivalent" upon production of prototypes within the application domain of the project targeted chemicals, *e.g.* food contact materials, cosmetics and medical devices.

A workshop on "*The role of* in silico *tools in supporting the application of the substitution principle*" has been organized last December 2014 in Milan by the project beneficiary Emilio Benfenati (Istituto Ricerche Farmacologiche "Mario Negri" - IRFMN). The state-of-the-art of different *in silico* methodologies were presented by experts from academia and industry. Pros and cons as well as the complementarity and application domain of the different *in silico* approaches were discussed, including the comparison and integration of (Q)SAR and read across approaches in regulatory domains (REACH, cosmetics regulation). LIFE-EDESIA could represent a step forward of the use of *in silico* tools, by implementing their role as screening and decision-making tool for identifying potential alternative to EDC going to further *in vitro* testing. The workshop was attended by about 40 participants with different expertise and the proceedings will be soon available on the project's website.

S. Lorenzetti & A. Mantovani,
life.edesia@iss.it

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The Russel and Burch Award

Dr. Martin Stephens, CAAT, was honoured by his peers with the Russell and Burch Award, presented by The Humane Society of the United States to scientists who advance alternative methods to animal testing and promote the 3Rs. The award is named in honour of William Russell and Rex Burch, the scientists who formulated the 3Rs approach and authored the classic text, *The Principles of Humane Experimental Technique*. Stephens was chosen as a clear standout for the award by his peers in the field as judged by 13 past winners. The award, which comes with a trophy and a $10,000 prize, was presented at the 9th World Congress on Alternatives and Animal Use in the Life Sciences, which was held in Prague, August 24-28, 2014.

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The 2014 LUSH Prize

The LUSH Prize honours the work of exceptional individuals, groups, or organizations for outstanding work towards non-animal testing. Amongst the 2014 awardees CAAT-Europe's Policy Program was awarded the LUSH Prize for Lobbying. CAAT promotes the development and implementation of alternative methods in safety testing over 33 years of history, and has policy programs in Washington since 2006 and in Brussels since 2012. The centre received the prize for its commitment to providing scientific information and expertise to policy makers. Thomas Hartung, Director of CAAT-US and François Busquet, who coordinates the scientific information activities of CAAT-Europe in Brussels, accepted the prize on November 14, 2014 in London.

Prof. Roland Grafström and Dr. Pekka Kohonen from the Karolinska Institute in Sweden were awarded the LUSH Science Prize. The scientists project has developed a cancer biology work and Tox21 Century-inspired approach for replacing toxicity testing in animals with informatics-driven data analysis of human cell cultures exposed to toxic agents. The role of the team has been to guide the application, analysis, interpretation and storage of so called "omics" technology-derived data within the SEURAT-1 subproject "ToxBank".

Prof. Ovanes Mekenyan from the laboratory of mathematical chemistry, Bulgaria, was awarded the LUSH Training Prize for his work on molecular modelling. Finally, a number of LUSH Young Research Awards were provided to:

- Róber Bachinski, Fluminense Federal University, Brazil;
- Thit Aarøe Mørck, University of Copenhagen, Denmark;
- Dr. Henrik Johansson, Lund University, Sweden;
- Anne Krug, University of Konstanz, Germany; and
- Jonathan Nicolas, Wageningen University, Netherlands.

For more information please consult: http://www.lushprize.org

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The 2015 SOT Enhancement of Animal Welfare Award

The Society of Toxicology (SOT) has awarded CAAT-Europe co-director Marcel Leist its **2015 Enhancement of Animal Welfare Award.**

The award honours an SOT member for contributions made to the advancement of toxicological science through the development and application of methods that replace, refine, or reduce the need for experimental animals. Dr. Leist's laboratory focuses on *in vitro* toxicology, specifically mechanisms and systems related to neurotoxicity.

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MEP-3Rs Scientists Pairing Scheme (EU Parliament)

The Centre for Alternatives to Animal Testing-Europe (CAAT-Europe) has announced a new initiative for better visibility of 3Rs issues in the Brussels policy arena. This initiative pioneers a close and strong relationship of scientists with their elected national members of the European Parliament (MEPs). This initiative will be supported by the MEPs under the title "MEP—3Rs scientist pairing scheme." MEPs will be paired with 3Rs scientists from their country. The MEP will benefit from the scientists' knowledge, while also enabling support for national 3Rs initiatives and funding schemes, as well as promoting them at the EU level.

This activity will be under the patronage of MEP Pietikainen (Finland). MEPs from France, the Czech Republic, Romania, Italy, Denmark, Germany, Sweden, and The Netherlands have already shown interest in such a network and many more are expected. A launch event for the network is tentatively planned for January 27th, 2015 during a reception titled "MEP—3Rs scientist pairing scheme" at the European Parliament in Brussels. The scientists will meet before the reception for a workshop to discuss and prepare a report, which will be published in *ALTEX* and will list the participants as co-authors. This initiative also provides the opportunity to be introduced to the policy-making process at the European Parliament and key European institutions.

A yearly meeting with the network would then take place to share best practices from each country (e.g., 3Rs communications to lay audience, 3Rs success stories, etc.). For more information, please contact: caat-eu-policy@uni-konstanz.de

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Highlights

The OECD has just published in February 2015 two new *in vitro* and *in chemico* Test Guidelines on human health hazard endpoint skin sensitisation. Skin sensitisation refers to an allergic response following skin contact with the tested chemical, as defined by the United Nations Globally Harmonized System of Classification and Labelling of Chemicals (UN GHS). Test Guideline 442C concerns an *in chemico* procedure for the Direct Peptide Reactivity Assay (DPRA) and addresses the molecular initiating event leading to the skin sensitisation. Test Guideline 442D looks at an *in vitro* procedure, namely the ARE-Nrf2 luciferase test method, and looks to address the second key event on the adverse outcome pathway leading to skin sensitisation. Both of these Test Guidelines set out the procedures for supporting the discrimination between skin sensitizers and non-sensitizers in accordance with the UN GHS. They are the first two in a series of *in vitro* methods that will gradually replace *in vivo* animal Test Guidelines on skin sensitisation; more of these alternative methods are detailed in the work plan of the Test Guidelines Programme. For more information, please consult: http://www.oecd-ilibrary.org/environment/

oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788

The OECD has also recently published the following Guidance Documents:

- Guidance Document n. 203 on an Integrated Approach on Testing and Assessment (IATA) for skin corrosion and irritation
- Guidance Document n. 207 on new scoping document on in vitro and ex vivo assays for the identification of modulators of thyroid hormone signalling
- Guidance Document n. 211 for describing non-guideline *in vitro test* methods

More information on the OECD published Guidance Documents can be found at: www.oecd.org/env/ehs/testing/seriesontestingandassessmentpublicationsbynumber.htm

New glossary of Reference Terms for Alternative Methods and their Validation

This new glossary, first published in ALTEX and now available on Altweb, provides technical references to support work in the field of alternatives to animal testing. Giving the ever-increasing number of alternative test methods and approaches being developed over the last decades, a combination, revision, and harmonization of earlier published collections of terms used in the validation of such methods was required. This glossary has the intention to provide guidance on issues related to the validation of new or updated testing methods consistent with current approaches. Moreover, because of new developments and technologies, a glossary needs to be a living, constantly updated document. The Internet-based version based on this compilation can be found on Altweb, allowing the addition of new material.

Meetings & Workshops Calendar

25-27 February 2015
4th Galenus Workshop: Drug Delivery to Human Skin Saarbrücken, Germany
www.uni-saarland.de/lehrstuhl/lehr-lab.html

22-26 March 2015
SOT - 54th Annual Meeting and ToxExpo
San Diego, California, US
http://www.toxicology.org/ai/meet/am2015/registration.asp

26 March 2015
EBTC SOT Satellite Meeting Updates on Activities Related to 21st Century Toxicology and Evidence-based Toxicology: Invited Presentation and Open Microphone San Diego, California
http://www.ebtox.com/sot2015ebtc/

25 March 2015
Biology meets Technology: Organ-on-a-Chip & Biosensors INVITROM Symposium
Breda, The Netherlands
http://www.invitrom.org

8-9 May 2015
International Conference of Alternatives to Animal Experimentation, Portugal
http://icaae.com/

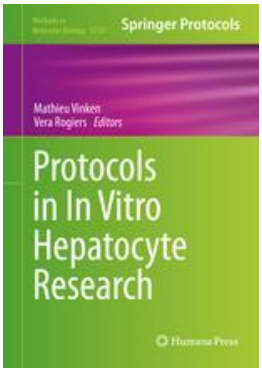
5 June 2015
3Rs Workshop Cluj-Napoca, Romania
http://rocam.usamvcluj.ro

9-15 July 2105
Second Latin-American Congress on Alternative Methods in Testing, Research, Industry and Education – COLAMA 2015
Varadero, Cuba
http://www.colamacuba.com/

13-16 September 2015
EUROTOX - 51th Congress of the European Societies of Toxicology Porto, Portugal
www.eurotox2015.com

13-15 October 2015
SSCT-Swetox Workshop
Järna, Sweden
http://www.ssct.se

New book release



ESTIV Vice-President Mathieu Vinken and ESTIV member Vera Rogiers, both affiliated to the Department of *In Vitro* Toxicology and Dermato-Cosmetology of the Vrije Universiteit Brussel, Belgium, have recently edited a book entitled '*Protocols in In Vitro Hepatocyte Research*' published by Springer (ISBN 978-1-4939-2073-0). This book presents 30 state-of-the-art protocols and reviews to set up and apply primary hepatocyte cultures for research and screening purposes. The first part of the book focuses on the use of these particular liver-based *in vitro* models to study the different aspects of the hepatocyte life cycle, including cell growth, differentiation and cell death. The second part of the book is targeted towards the demonstration of the applicability of primary hepatocyte cultures, or liver-based *in vitro* models derived thereof, for functionality and toxicity testing. Written in the highly successful '*Methods in Molecular Biology*' series format (volume 1250), chapters include introductions to their respective topics, lists of the necessary materials and reagents, step-by-step and readily reproducible laboratory protocols, and key tips on troubleshooting and avoiding known pitfalls.
More information can be found *via* the following link:
http://www.springer.com/biomed/pharmacology+%26+toxicology/book/978-1-4939-2073-0

Predictive Toxicology: From Vision to Reality, editors: F. Pfannkuch and L. Suter-Dick, Series Editors: Raimund Mannhold, Hugo Kubinyi, Gerd Folkers, John Wiley & Sons, 2014

Recent Publications of ESTIV members

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Toxicology *in vitro*

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Editors: Daniel Acosta,

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Laura Suter-Dick

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