Corners

CAAT feed

Thomas Hartung Discusses Rising Numbers of Monkeys in U.S. Research (*Science*)

From Science:
The total number of monkeys in research labs has not changed much in the past few years, but more are being used in studies.

That forecast frustrates Hartung, who says NIH should launch a review of the need for monkeys, similar to the one that led it to end its support for chimpanzee research. He challenges the idea, for instance, that nonhuman primates are more useful for drug testing than rats or mice. Nonhuman primates are more genetically variable than rodents, he argues, and researchers typically use relatively few monkeys for studies of drug efficacy and safety. As a result, those experiments could yield skewed data on how the drugs will act in humans. Scientists embracing monkey experiments, he says, are at risk of "repeating the mistakes of the past."

https://www.sciencemag.org/news/2018/11/record-number-monkeys-being-used-us-research

Making Big Sense from Big Data

Thomas Hartung has recently assumed the editorship of Public Health and Medicine for Frontiers in *Big Data* and *Frontiers in Artificial Intelligence*.

From his editorial:
"But the point is not about generating or storing Big Data – it's about squeezing sense out of them. It is about how to ensure the quality of data and the relevance of results. We need a culture of quality control and quality assurance, and of good practices, especially when having to trust machines to derive our results. ...

We have a moral obligation to deliver the right results and communicate them with their very real limitations to society and policy-makers. It is too easy to impress with big numbers and too difficult for non-experts to cross-check – big data need to adhere to clear standards of truthfulness and reliability."

Hartung, T. (2018). Making big sense from big data. *Front Big Data 1*, 5. doi:10.3389/fdata.2018.00005

Keynote by Andrew Rowan, PhD: The Origins of CAAT and its Impact Over the Years: An Animal Advocate Viewpoint

Dr Rowan was the founder and first and longest-serving director of the Tufts Center for Animals and Public Policy (1983-1997). His history with animal research issues dates back to a stint at FRAME (Fund for the Replacement of Animals in Medical Experiments) in London (1976-1978). He continued his involvement at the Humane Society of the United States (HSUS), where he was vice president for animal research issues (1978-1982) and where he served as Chief Scientific Officer of HSUS and President and CEO of Humane Society International until his recent retirement.

The keynote talk took place November 28 in Baltimore and kicked off CAAT's fall board meeting. Dr Rowan discussed the origins and evolution of CAAT and its continuing impact on scientific research and animal welfare.

You can watch the keynote in its entirety here: https://youtu.be/ZBxp-lq7-oY

Book Launch *Animal Experimentation: Working Towards a Paradigm Change*

Russell and Burch introduced the principles of replacement, reduction, and refinement of animal experimentation in 1959 in their groundbreaking book, *The Principles of Humane Experimental Technique*. Their highest goal was to avoid the use of animals wherever possible, and – in cases where animals were still deemed indispensable – to significantly enhance their treatment while also improving the quality of research and testing. There is growing recognition that a focus on human-relevant data is needed for the understanding and possible treatment of chronic, complex diseases, many of which are not well understood and, thus, cannot be readily modeled in other animals. The technology revolution has greatly changed the field of life sciences and now provides us with tools enabling a shift away from animal experimentation.

The 51 experts who contributed to *Animal Experimentation: Working Towards a Paradigm Change* review current animal use in science, present new and innovative non-animal approaches to address urgent scientific questions, and offer a roadmap towards the continuing replacement and eventual elimination of animals used in science as envisioned by Russell and Burch almost 60 years ago.

CAAT's Assistant Scientist and Veterinarian Kathrin Herrmann is one of the book's editors. Thomas Hartung contributed the concluding chapter.

At this book launch event, which was held on November 30 at the Bloomberg School of Public Health, several of the mostly North America-based authors gave talks based on their book chapters. You can watch the entire series of talks here: https://youtu.be/CRGCviK8IvM

ESTIV 2018 in Berlin Sets Records

The 20th International Congress on In Vitro Toxicology (ESTIV2018) was co-hosted by the European Society of Toxicology In Vitro (ESTIV), the German Toxicology Society (GT), and CAAT-Europe. The general theme of the Congress was "new approach methodologies for *in vitro* toxicology applications," which was fully reflected in the eight thematic sessions. 447 participants came from 45 countries (18% from industry, 19% students). 285 submitted abstracts plus invited presentations led to 43 oral and 233 poster presentations, which set records for the event.

CAAT Offers New Online Course in Evidence-based Toxicology

In medicine and healthcare, evidence-based medicine has revolutionized the way that information is evaluated transparently and objectively. Over the past ten years, a movement in North America and Europe has attempted to translate this revolution to the field of toxicology. The Center for Alternatives to Animal Testing (CAAT) hosts the first chair for Evidence-based Toxicology (EBT) and the secretariat for the EBT Collaboration on both sides of the Atlantic. Based on the Cochrane Collaboration in Evidence-based Medicine, the EBT Collaboration was established at CAAT to foster the development of a process for quality assurance of new toxicity tests for the assessment of safety in humans and the environment.

Systematic review and related evidence-based approaches are beginning to be adapted by regulatory agencies like the Environment Protection Agency (EPA), the European Food Safety Authority (EFSA), and the US National Toxicology Program. They provide transparent, objective, and consistent tools to identify, select, appraise, and extract evidence across studies. This course will showcase these emerging efforts and address opportunities and challenges to the expanded use of these tools within toxicology.

The course is free and available via Coursera (https://www.coursera.org/learn/evidence-based-toxicology).

CAAT also offers an online course on Toxicology 21: Scientific Applications (https://www.coursera.org/learn/toxicology-21), which has had over 1,000 enrolled learners since its release in March 2018.

Thomas Hartung at Frontiers Forum 2018: No More Lab Rats? (Video)

Can animal testing be eliminated? Thomas Hartung examines the future of toxicity testing, including the use of big data and human *in vitro* models.

As part of his efforts to drive a paradigm shift in toxicity testing to improve public health, Thomas developed lab-grown "mini-brains" from human stem cells as an alternative to animal models for testing new drugs. His team also created the largest machine-readable toxicological database – allowing toxicity predictions by machine learning that outperform lab animals.

Video (YouTube): https://www.youtube.com/watch?v=VcrknGTZxyY

New Publications

Grinberg, M., Stöber, R. M., Albrecht, W. et al. (2018). Toxicogenomics directory of rat hepatotoxicants in vivo and in cultivated hepatocytes. *Arch Toxicol 92*, 3517-3533. doi:10.1007/s00204-018-2352-3

Luechtefeld, T., Marsh, D. and Hartung, T. (2018). Missing the difference between big data & artificial intelligence in RASAR versus traditional QSAR. *Toxicol Sci 30*. doi:10.1093/toxsci/kfy287

Maertens, A., Tran, V., Kleensang, A. and Hartung, T. (2018). Weighted Gene Correlation Network Analysis (WGCNA) reveals novel transcription factors associated with bisphenol a dose-response. *Front Genet 9*, 508. doi:10.3389/fgene.2018.00508

Gutbier, S., Spreng, A. S., Delp, J. et al. (2018). Prevention of neuronal apoptosis by astrocytes through thiol-mediated stress response modulation and accelerated recovery from proteotoxic stress. *Cell Death Differ 25*, 2101-2117. doi:10.1038/s41418-018-0229-x

Cruelty Free INTERNATIONAL
Ending animal experiments worldwide

Coty's COVERGIRL becomes the largest makeup brand ever to go cruelty free

On November 4, Cruelty Free International announced a new partnership with Coty, one of the world's leading beauty companies, that aims to end animal testing for cosmetics globally.

As a first step in the partnership, Coty has been awarded the Leaping Bunny certification for their beauty range COVERGIRL, making it the largest makeup brand to ever receive certification. The Leaping Bunny logo, which is the best visible and independent assurance for consumers of a company's commitment to end animal testing, will now feature on all COVERGIRL products.

Coty has already committed to at least one more of its brands being certified with the Leaping Bunny by 2020.

Over 80,000 signatures brought to Downing Street to end dog experiments in the UK

On November 21, Cruelty Free International took over 80,000 signatures to 10 Downing Street to call for an end to the use of dogs in UK laboratories.

Earlier this year it was announced that from January 1, 2020 experiments involving dogs, cats and primates will be forbidden in the Brussels-Capital Region of Belgium.

In 2017, almost 4,000 experiments were conducted on dogs in the UK, the majority of which were for regulatory purposes including testing of human and veterinary drugs and agricultural products. Cruelty Free International's "Lead the Way" campaign, which was launched earlier in the year, and has received support from multiple politicians and celebrities, calls on the Home Office to develop a roadmap that would see an end to the use of dogs in UK research by 2020.

New update on recently approved alternative methods for regulatory testing

In October, Cruelty Free International produced its second annual update on alternative approaches that have been approved for use within the last year for chemicals and pharmaceutical regulatory testing.

The update describes the 3Rs implications of new and revised guidelines and guidance documents produced by the Organisation for Economic Cooperation and Development (OECD), the EU Test Methods Regulation (EC/440/2008), the European Chemicals Agency (ECHA), the European Directorate for the Quality of Medicines & Healthcare (EDQM), the European Medicines Agency (EMA), the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and the International Conference on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH).

The European Commission has already shared this important update with all member states and stakeholders to promote the use of alternatives. To obtain a copy, please e-mail laura.alvarez@crueltyfreeinternational.org

Review published to highlight the effects of stress on animals in laboratories

Dr Jarrod Bailey, Senior Research Scientist at Cruelty Free International, has published a critical review in Alternatives to Laboratory Animals (ATLA), highlighting the effects of stress and distress on animals in laboratories.

His review claims that for animals in laboratories stress is frequent, significant, unavoidable, a result of unnatural events that would not be encountered in the animals' natural habitat, and is therefore far from benign. As such, it has adverse consequences for animal welfare and for many facets of data relevance and reliability due to effects on a wide range of physiological systems. He calls on the scientific community to engage with and address these issues more overtly and rigorously.

Bailey, J. (2018). Does the stress of laboratory life and experimentation on animals adversely affect research data? A critical review. *Altern Lab Anim 46*, 291-305.

Pilot project opens door for cruelty free companies to sell in China

Earlier this year, Cruelty Free International launched a ground-breaking pilot scheme to pave the way for Leaping Bunny certified cosmetics companies to sell their products in China and to encourage regulatory change in China.

Leaping Bunny certification currently excludes export to China because of existing mandatory animal testing for importing cosmetics. By partnering with Knudsen&Co, Oriental Beauty Valley and Shanghai Fengpu Industrial Park, the new project will help remove the remaining barriers of entry for cruelty free cosmetics brands looking to manufacture and market their products in China. International brands will be able to avoid testing on animals by producing cosmetics in China that do not need post-market testing.

On November 20, the first Leaping Bunny companies that will be part of this collaborative venture were announced. Longstanding Leaping Bunny brands Bulldog Skincare, Neal's Yard Remedies, Seventh Heaven and Subtle Energies will now be able to maintain their cruelty free status while pursuing production in China free from the risk of post-market testing.

EUSAAT

European Society for Alternatives to Animal Testing

The 21st European Congress on Alternatives to Animal Testing in Linz 2018 was a great success

The congress, which was also the 18th Annual Congress of EUSAAT – EUSAAT 2018, took place on September 23-26 at the Johannes Kepler University in Linz, Austria.

Several aims and expectations were exceeded. The low registration fees were retained, approximately 300 participants attended the congress. One major goal was to provide a comprehensive communication platform covering all different aspects and groups from the 3Rs field. Another major intention was to support and attract especially young scientists and to bring the 3Rs centers together and encourage communication. Moreover, critical discussions about the development of the 3Rs world, European and international movements, scientific and technological advancements, but also personal success stories of trailblazers in the field contributed, together with extraordinary efforts for a friendly environment, to the high quality of the meeting. But now the more detailed facts:

Organizers and Supporters

The congress was organized by EUSAAT, the European Society for Alternatives to Animal Testing, supported by the Austrian Federal Ministries BMASGK, BMBWF, BMNT, the large research institution AIT, the Austrian Institute of Technology GmbH, the University of Veterinary Medicine Vienna, the FH Technikum Wien as well as the German FU Berlin and the Czech National Institute of Public Health. Moreover, the congress was also supported by several international scientific societies and organizations such as the German Animal Welfare Association, the German SET Foundation, ASCCT from the USA, the Chinese Centre for Alternatives Research and Evaluation, and the Japanese Society for Alternatives to Animal Experiments.

Participants

A total of just over 300 attendees took part, again from a wide variety of disciplines: from basic researchers, physicians, veterinarians, and (bio)-technologists to ethicists, philosophers, and lawyers. Very importantly, the EUSAAT congress again aimed to attract many representatives of 3R-relevant stakeholders such as government authorities, industry, universities, and animal welfare organizations. The participants represented 29 countries, mostly from Europe, including Germany, Austria, France, Italy, UK, Benelux, Scandinavian countries, but also the USA, Japan, and China. The congress was predominantly female: 194 women and 117 men (62%:38%). This is a very positive development with regard to promoting women in the life sciences.

Topics

As usual for this congress, the spectrum of topics was very broad and ranged from "3D Models & Multi-Organ-Chips (MOCs), Human-Organ-Chips (HOCs)" to topics directly relevant for consumers such as "Advanced Safety Testing of Cosmetics and Consumer Products", "Alternatives to Animal Testing in Food Safety" and "Nutrition and Efficacy" as well as to the topics "Biological Barriers", "Disease Models Using Human Cells, Tissues and Organs", "Efficacy and Safety Testing of Drugs, Medical Devices & Biopharmaceutics", "*In Silico* Models: Toxicology & Efficacy of Drugs, Chemicals & Cosmetics", "*In vitro* Techniques for CNS Toxicity and Disease Studies" and "Vaccines & The 3Rs: New Methods and Developments (e.g., Batch Release Testing)".

In total, 169 oral presentations were given in 33 sessions and 99 posters were presented in two poster sessions.

In order to inform and reflect about current trends and developments observed during the EUSAAT 2018 congress, the following topics are highlighted:

"*3D models/human organ chips*": The importance as well as the potential sustainability of the presented methods was shown by the fact that this topic had to be split into five single sessions due to the high number of accepted oral presentations. The topic comprises high-level biotechnology, which focuses on the use of human cells in cell culture systems that ideally function completely without animal components, i.e., also without fetal calf serum. The objective here is to create microphysiological systems with complex multicellular structures in order to study the development of organs, to assess the role of the individual cell types for complex physiological and pathophysiological processes, and to combine multicellular structures simulating an organ with others to arrive at multiorgan-mimicking systems, which may be used for complex pharmacokinetic studies. Ideally, MOC models should be based completely on human material, which would eliminate the enormous problem of transferability of data obtained with animals to human data.

The "*Disease Models*" topic was particularly important. Three sessions on disease models focused on the recent progress especially in diseases of the lung and infectious diseases, skin diseases, and cancer. The trend is to complement or replace models of animal origin, and thus also animal cell culture models, with human cell-based models. Again, this would eliminate the problem of data transferability from animals to humans while also decreasing or even replacing animal use. The fact that in some instances animal experiments are still a topic in the *cosmetics* sector was underlined in the session on this subject. The relevance of alternatives to animal tests in the fields of *nutrition* and *ecotoxicology* may not be sufficiently perceived, but is ultimately of great importance to the general public. EUSAAT 2018 reserved room for these topics and their growing significance was reflected in three sessions with lively discussion and scientific exchange. In addition, exciting sessions about "*Specific*

Endpoints in Toxicity" and "*Stem Cell Models*" were on the agenda.

The Linz congresses as the European 3Rs congresses cover each of the 3Rs comprehensively; this means specific sessions on *refinement, reduction* and *replacement*. For example, improvements and progress in the area of animal husbandry were put into focus as these can reduce or avoid stress to and suffering of experimental animals. Another important aspect was the 3Rs in the field of education and training.

Three *round tables* about "International Progress in 3Rs Research", "3R Centers in Europe – National and Local Centers" and "Applying Human 3D Models and Multi-Organ-Chips (MOCs) in Industry" with esteemed international experts as moderators and panelists from authorities, 3Rs centers and societies, and industry provided insights into current developments and future needs to bring the 3Rs matters forward.

Young Scientist Travel Award

To promote young scientists working in the 3Rs field, a Young Scientist Travel Award was announced for the third time with the support of the German SET Foundation and TissUse GmbH. From almost 50 submissions, 20 scholarship holders were selected and encouraged this year to present their results in Linz in two special Young Scientists sessions and to engage in discussion. The three best YSTA presentations were awarded a special prize. We congratulate Michelle Hesler (Fraunhofer Institute for Biomedical Engineering, Sulzbach, Germany with "Human buffy-coat derived platelet lysate: comparison of single-patient and pooled units for the cultivation of different human cell lines"), Carolin Drieschner (Eawag, Dübendorf, Switzerland with "FISH on CHIPS: Development of a novel *in vitro* system of the fish intestine"), and Katharina Hörst (FU-Berlin, Berlin, Germany with "Co-cultivation of myofibroblasts and adipocytes provides new insights into hypertrophic scar regeneration").

Collaboration and networking in the 3Rs field at EUSAAT 2018

Progress in the 3Rs field needs exchange and cooperation. In recent years, new 3R centers have been created in Europe. An extra meeting was organized at the congress to provide the opportunity for representatives of these centers to get to know each other personally, to exchange ideas, and to discuss future cooperation.

Following the tradition of the last congresses, the prestigious ALTEX Prize 2018 (doi:10.14573/altex.aaw) for the best paper published in ALTEX in the previous year was awarded at the social evening of the EUSAAT Congress in Linz by Dr Sonja von Aulock.

Advanced Training

Following the congress, a training workshop – free for the congress participants – was offered and organized as an EUSAAT 2018 Practical Training Course on Alternative Methods: "EUSAAT 2018 – Kirkstall Quasi Vivo® Training Workshop". The course consisted of 2 half days including lectures and practical training.

Publications

The abstracts of the lectures and posters were made available in advance and can be accessed on the congress website (http://eusaat-congress.eu) and on the ALTEX Proceedings website (doi:10.14573/altex.apr).

Save The Date

We are very much looking forward to meeting you at the EUSAAT 2019 on August 25-28, 2019 at the Johannes Kepler University in Linz, Austria.

EU-ToxRisk

The EU-ToxRisk project is at an exciting turning point!

In the first three years of the project, all partners worked hard to refine a novel new approach method (NAM)-based testing approach, supported by the scientific and regulatory advisory boards of the project. Progress was made along two dimensions: (i) hazard evaluation, used from the quantity point of view, with state-of-art test methods for compound bioactivity and ADME properties; (ii) a quality assurance pipeline development to ensure validity and reproducibility of test methods and data handling procedures according to FAIR (findable, accessible, interoperable and re-usable data) criteria.

Now it is finally time for EU-ToxRisk to enter into a new phase and to open up to the outside.

The consortium has developed a commercialization pipeline that can feed methods expertise into a state-of-the-art service package for innovative chemical safety assessment. The EU-ToxRisk project aims to offer a range of "products" to the scientific, regulatory and industrial communities:

- *Novel methods*. The expertise in *in silico* modeling (including toxicokinetic modeling, chemo- and bioinformatics), innovative high throughput platforms, advanced organ-specific assays, and broad toxicological expertise will be integrated into pragmatic testing strategies for chemical risk assessment. It is planned that integrated service and test packages will be offered also beyond the runtime of the project in form of a self-sustaining cross-company commercialization platform.
- *Read-Across (RAx) guidance*. As a result of the strong network developed between the EU-ToxRisk consortium and regulatory agencies, which has allowed the refinement of a read-across strategy and reporting template, the guidance, together with the creation of a web-based graphical user inter-

face, will be shared with the toxicological community with the main goal being to improve the quality of the submissions of real read-across cases by registrants and eventually increase the success rate of non-animal approaches developed by industry.

- *Industry joint case studies*. The integrative approach, developed thanks to this unique combination of expertise and test methods, together with the experience in regulatory submission, allows the EU-ToxRisk team to support external industry partners. Such joint case studies may allow identifying toxic hazard, helping to inform strategic decisions, prioritizing chemicals within a group, evaluating new approaches, and supporting the problem-solving process of investigative toxicology.

EU-ToxRisk publications

The most recent EU-ToxRisk publications describe the broad toxicological approach developed by the consortium in the context of novel technologies and of quality assurance (QA) procedures applied to *in vitro*/*in silico* test methods.

An example of the application of a quality assurance workflow to *in silico* QSAR tools was described by Gadaleta et al. (2018). The authors designed a semi-automated workflow to integrate structural data retrieval, automated data comparison, chemical structure cleaning, and data selection and standardization. Application of such a QA procedure is critical for proper use of QSAR tools and for their use to explore complex endpoints. As described in another recent publication by the same group (Gadaleta et al., 2018b), a QSAR modeling approach has now been utilized to explore the adverse outcome pathways underlying induction of hepatic steatosis by prediction of its molecular initiating events.

The use of QA approaches is also widely applied to *in vitro* test method development. In Gutbier et al. (2018), the authors showed how not only chromosomal aberrations and mutations in single pivotal genes but also minor, possibly pleiotropic, genome changes can have drastic effects on biochemical features and toxicological responses of relatively similar cell subpopulations.

Gu et al. (2018) address a central scientific topic of EU-ToxRisk: How long do *in vitro* experiments need to run to predict human repeated-dose toxicity? They explored how the variation of the incubation period of a test compound can significantly influence the results of *in vitro* tests. Different treatment periods have been compared with the aim to identify the test conditions that would best correspond to human repeated-dose toxicity.

Innovative technologies such as high content imaging and high-throughput transcriptome analysis have been applied to investigate pathways of toxicity. An example is represented by the Nrf2 pathway and its response to chemical insult. Bischoff et al. (2018) made use of single cell live imaging to quantitatively monitor the dynamics of the Nrf2 pathway during repeated toxic exposure, taking advantage of engineered fluorescent protein reporter cell lines. In Copple et al. (2018), microarray technology was applied to perform weighted gene co-expression network analysis and explore perturbations of the Nrf2 transcriptional network. A major understanding of the pathway will improve the prediction of clinical toxicities such as drug-induced liver injury.

Finally, an advanced organ-specific assay was established and described by Gutbier et al. (2018). A well-established model of postmitotic human dopaminergic neurons (LUHMES cells) was used in the absence of or in co-culture with astrocytes to investigate the mechanisms involved in the endogenous neurodefensive activity of astrocytes. The presence of astrocytes attenuated the neuronal stress response, increasing neuronal resilience to various proteotoxic stressors. Such knowledge not only applies to toxicological predictions, but may also allow boosting of the brain's own defense mechanisms and could be used to increase the brain's resilience towards toxicants or the progression of neurodegenerative disease.

Outlook

The different novel methods and approaches of the EU-ToxRisk project will be presented at the upcoming open symposium at the yearly general assembly (Zuiderduin hotel, in Egmond aan Zee, The Netherlands) on February 12-13, 2019. Stakeholders from industry, regulatory organizations and academia will have the opportunity to meet the partners of the projects and discuss novel technologies and approaches for risk assessment.

The RAx guidance will be discussed at the "Read-across Workshop" in Helsinki on May 21-22 2019, an event organized by EU-ToxRisk with the help of ECHA and regulatory colleagues from other authorities (EFSA, NTP, EPA, OECD, SCCS). The feedback from this workshop will be used to finalize a comprehensive publication on NAM-based read-across.

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Giorgia Pallocca and Marcel Leist