Inauguration of CAAT-EU – a memorable start to a transatlantic collaboration

University of Konstanz, 30th March 2010

The Center for Alternatives to Animal Testing-Europe (CAAT-EU) is a joint venture of the Johns Hopkins University in Baltimore, USA, and the University of Konstanz in Germany. It was created as a communication platform for science, industry, regulatory authorities, and animal welfare organizations in Europe and the US. This transatlantic venture will promote the application and teaching of humane science, raise funds from industrial and private sponsors for this purpose, and participate in and/or coordinate EU-funded projects. Working together, CAAT and CAAT-EU promise sound scientific synergy involving experts from both sides of Atlantic to promote the implementation of human-relevant alternative approaches, the advancement of research in this field, and the dissemination of the 3Rs

The inaugural ceremony took place on March 30th 2010 in the Senate Hall of the University of Konstanz. In addition to the directors of CAAT and CAAT-EU, the list of speakers included University representatives, cooperation partners, supporters from industry and science, and the animal welfare organization Eurogroup for Animals, as well as the three designated "Patrons of alternative methods."

The Senate Hall was packed with 120 guests. The mild weather and views of snow-capped Alps and sparkling Lake Constance provided a memorable atmosphere. **Ulrich Ruediger**, the rector of the University of Konstanz, gave the welcome speech, which described the university's focus on Life Sciences. He was followed by **Thomas Hartung**, director of CAAT, co-director of CAAT-EU, and professor at both universities, who initiated of the formation of CAAT-EU. His talk offered an introduction to the US concept of a "Toxicology for the 21st century" (Tox-21c), which has stirred tremendous interest and excitement in the field. Hartung introduced the rationale for human-relevant alternative methods and explained the inadequacies of the initial calculations carried out for REACH. Hartung quoted Francis Collins, now director of the NIH: "We propose a shift from primarily *in vivo* animal studies to *in vitro* assays, *in vivo* assays with lower organisms, and computational modeling for toxicity assessments … (Toxicity testing) was expensive, time-consuming, used animals in large numbers, and didn't always work." **Michael Klag**, Dean of Johns Hopkins Bloomberg School of Public Health, discussed the significance of public health in the US, emphasizing the role of the Johns Hopkins Bloomberg School in medical research and also in funding of international research and aid programs.

Alan Goldberg, former director of CAAT and chairman of the CAAT board, used the example of the Draize Test on rabbit eyes to demonstrate the advantages of *in vitro* methods and the inaccuracy of animal models. As one of the "patrons of alternative methods in the life sciences" appointed by the 2009 World Congress on Alternative Methods in Rome, he gave an insider's overview of the success story CAAT's push for alternatives over the last three decades. He stressed the necessity and importance of *in vitro* toxicology and the role of transatlantic cooperation.

Marcel Leist, director of CAAT-EU and Doerenkamp-Zbinden chair for *in vitro* toxicology and biomedicine at the University of Konstanz, detailed the scope and functions of CAAT-EU: 1) coordination of research consortia; 2) installa-

tion of a dynamic CAAT-EU faculty and advisory board to address topical issues; 3) organization of information days on relevant developments in the US and Europe; 4) strategic project development; and 5) joint education programs. Moreover, he outlined plans for the Transatlantic Think Tank of Toxicology (t^4).

Both universities participating in the CAAT-EU venture have a history of collaboration, as **Gerd Gantefoer**, professor of physics in Konstanz and research professor at Johns Hopkins explained in a lively and informative talk. He described the difficulties but also the value of his experiences collaborating in a joint research project on nanomaterials for energy storage and energy conversion.

Michael Balls, emeritus Professor for Medical Cell Biology at the University of Nottingham, trustee of the Fund for the Replacement of Animals in Medical Experiments (FRAME), Editor of *ATLA*, and a second patron of alternative methods, was one of the highlights of the ceremony with his speech, "Alternative methods, servant to two masters." Balls advised CAAT-EU to be aware of conflicts of interest, to compete by putting forward new ideas, to collaborate in putting the most innovative concepts into practice, to join in leading the "revolution," and to contribute to the improvement of hazard prediction and risk assessment by developing, validating, and employing advanced methods and replacing the use of flawed animal tests.

Horst Spielmann, retired head of the National German Centre for the Documentation and Evaluation of Alternatives to Animal Testing (ZEBET) and professor for regulatory risk assessment at the Free University of Berlin, and the third patron of alternative methods, presented his vision of the future of developmental toxicology. Spielmann spoke of the need for harmonization of reproductive toxicity testing across all sectors of regulatory testing, of exposure-driven testing of industrial chemicals, the implementation of a new "extended one-generation reproductive toxicity study" and other *in vitro* methods for toxicity testing in the 21st century. As examples, he pointed to the ReProTect *in vitro* battery and the embryonic stem cell technology focusing on molecular endpoints in both the murine and human stem cell test.

Congratulatory greetings from sponsors, supporters, and partners rounded out the inaugural festivities. **Adela Lopez De Cerain**, president of ECOPA, discussed the structure of the European Consensus Platform. The participating National Consensus Platforms are Austria (ZET), Czech Republic (CZECOPA), The Netherlands (ZonMw), France (within Inserm), Germany (SET), Hungary (HUCOPA), Italy (IPAM), Spain (REMA), Belgium (BPAM), Denmark (DACOPA), Finland (FINCOPA), Norway (NORECOPA), Sweden (SWECOPA), Switzerland (3Rs Research Foundation), and Poland (POLCOPA).

Kirsty Reid, policy officer for research animals of EuroGroup for Animals, gave an overview of the activities of European organizations working in the 3Rs. She stressed that a paradigm shift is needed to accomplish scientific improvements and safety testing without the reliance on animals and with more emphasis on the research, implementation, and enforcement of 3Rs.

Franz P. Gruber, president of the Doerenkamp-Zbinden Foundation (DZF), described the establishment of the foundation 25 years ago and its activities and continuing support of alternative methods to animal experimentation in biomedical research and education. The foundation, in recognition of the importance of academic research, has established six academic chairs in Germany, Switzerland, USA, the Netherlands and India, and is supporting CAAT and CAAT-EU. Gruber spoke enthusiastically about the University of Konstanz, with its 20-year tradition of research on alternative methods and the unique scientific focus of the Faculty of Biology, as the ideal place for the installation of CAAT-EU.

Robert Landsiedel, head of acute toxicity, experimental toxicity and ecology at BASF, discussed his organization's application of alternative methods. He reported that 20 alternative methods are currently in use at BASF, with 35% of all toxicological studies performed using alternative methods. The first lab converted for exclusive use of alternative methods has been installed. BASF has also developed a screening strategy for agrochemicals and alternative testing strategies for cosmetic ingredients, and sponsors CAAT-EU.

Didma de Groot, Senior Scientist in neurotoxicology and safety pharmacology at TNO, Zeist, The Netherlands, explained why TNO adopted alternative methods years ago. She stressed the need for sustainable testing approaches that contribute to the 3Rs, are more predictive for humans, less laborious, and faster than current methods..

After the official signing of the contract between the universities by Ulrich Ruediger and Michael Klag, the inauguration ended with a reception and a festive dinner at the Inselhotel in Konstanz.

The festive inauguration marks the starting point of the first transatlantic organization for alternatives. Fostering a dialogue and promoting conceptual work to reduce animal testing in safety assessments, agent discovery, and research is a global challenge that calls for in-depth collaboration. The caravan to 3Rs and Tox-21c now has a new CAATalyzer.

Mardas Daneshian

EPAA reinforces action on dissemination

2009 EPAA Annual Conference
Workshop on Dissemination

The European Partnership for Alternative Approaches to Animal Testing (EPAA) focussed on Dissemination of 3Rs information in its Conference on 6th November 2009. Besides some important recommendations for improving dissemination, the Conference demonstrated that, as EPAA moves into its fifth year, it has reached a new level of maturity. Not only has it advanced the knowledge and use of alternative methods, but it has stepped up to a new degree of impact and reputation.

European Commission Vice-President Günter Verheugen commented on the EPAA's evolution in his address to the conference. But above all, it is the decision to extend the activities of EPAA beyond its initial five years that shows that everyone involved with it now recognises the EPAA's value and potential.

The partnership has proven its value as an inclusive platform for dialogue and scientific collaboration and for tackling areas not taken up by other programmes or bodies, said Odile de Silva, the industry co-chair. Commission DG Enterprise and Industry Director Georgette Lalis expressed "definite interest" in continued cooperation. Industry participants further confirmed that, despite the current economic pressures, industry's commitment to the 3Rs and EPAA remains intact beyond the initial phase of five years.

The conference reviewed the EPAA's achievements in developing and transferring technologies that have the potential to lead to large reductions in the use of animals in research, and in improvements in communication with regulators and actions related to validation of alternative methods.

For an increased efficiency

To increase its efficiency and coordination, EPAA has reorganised its initial five working groups into three platforms: Science, Regulation and Dissemination.

The platform on Science will identify priorities for future research and spot the gaps and opportunities to improve animal welfare, including transferring opportunities across sectors. "We need sound science in order to base any new development in the 3Rs," said Odile de Silva.

But since science must be taken up to regulatory levels, and not just in Europe, the new platform on Regulation will continue the EPAA focus on overcoming barriers to regulatory acceptance, facilitating implementation and monitoring legislative developments.

The creation of a platform on Dissemination and communication is the logical response to bridging the current gap between knowledge and practice. There is at present no systematic process to ensure widespread uptake once a new method is accepted.

It is no longer sufficient, EPAA feels, to rely on *ad hoc* solutions and the dedication of individuals. The work of the taskforce on dissemination is being taken forward now by the new Dissemination platform.

Spreading knowledge

The Conference devoted most attention to a theme that has acquired increasing importance over the past four years: the need to spread knowledge about 3Rs advances among researchers, validators, regulators and test users – in a word, dissemination. The Conference therefore examined work carried out on dissemination and in particular the results of a workshop on this topic that was held on 5th November 2009 (see below).

Günter Verheugen himself made the point in his opening address: "It is essential that the potential of 3Rs and progress in the development of alternative approaches is brought to the attention of regulators and that those who work on the promotion of the 3Rs are aware of regulators' needs and requirements".

EPAA has always identified dissemination as a key issue. "It is in the background of all our activities and workshops," said Magda Chlebus from the European Federation of Pharmaceutical Industry Associations. Now dissemination is firmly embedded as a key stream of activity.

EPAA's 2009 Poster award highlighted dissemination

To reinforce the focus on dissemination of information on 3Rs, a thematic poster exhibition and competition was held as part of the EPAA 2009 Annual Conference.

EPAA invited companies, academia, research institutes and other organisations to provide posters describing, in lay lan-

guage, initiatives related to the dissemination of 3Rs information and expected 3Rs impact (enhancing 3Rs development, uptake and regulatory acceptance).

The aim of the poster session was to gather and highlight initiatives at national or international level, indicating synergies and complementarity between different approaches. In total, 13 posters were presented.

The 2009 award, a prize of € 1,500 to be used for 3Rs-related activities, was granted to M. Vivier and V. Rogiers of *ecopa* (the European Consensus Platform for Alternatives) for their poster: "ecopa, partner in dissemination of results in different EU projects".

- The winning poster can be viewed on the EPAA website at: http://ec.europa.eu/enterprise/epaa/4_events/ann_conf_2009/posters_13_v_rogiers.pdf
- The 2009 progress report is available on the EPAA website at: http://ec.europa.eu/enterprise/epaa/4_events/ann_conf_2009/annual_report_2009.pdf
- The full report of the conference is available at: http://ec.europa.eu/enterprise/epaa/4_2_conf_2009.htm

EPAA's Workshop on Dissemination of 3Rs information

(Brussels, 5th November 2009)

One of the key challenges in promoting the 3Rs is making sure that the available information gets out to those who can make use of it. That means the regulatory bodies, those in industry who are using animals in tests, but also the scientists who are actual or potential test developers. This was the challenge taken up by the EPAA workshop on Dissemination of 3Rs Information to Enhance Research, Acceptance and Uptake of 3Rs in Brussels on 5th November, which brought together industry, academia, regulators and organisations promoting 3Rs methods, concluding various activities throughout 2009 as an input to the 2009 Conference.

EPAA as a 3Rs market place for ideas

"You cannot use what you don't know about," Joachim Kreysa of the European Commission's Joint Research Centre told the workshop. The statement is simple, yet it encapsulates one of the key challenges in work on the 3Rs – making sure that the information that is available gets out to those who can use it. That means first and foremost the regulatory bodies, but not only them: it must also reach those in industry who are performing animal tests.

At the end of the workshop, the stakeholders present – from industry, regulators, users and bodies promoting 3Rs methods – were in broad agreement about what they need to know, how they need to know it, and how to encourage a greater flow of knowledge among and between them all.

The key concept that emerged was of a "3Rs marketplace" where the EPAA serves as what Phil Botham from Syngenta called an "honest broker service", bringing together researchers with ideas for possible new methods and industry and regulators looking for solutions.

The 3Rs marketplace is one of a raft of ideas that the workshop took forward to the EPAA conference the next day. These ideas were not suddenly invented by the workshop. They have been maturing over many months as part of a strategic examination by the EPAA of the issue of dissemination.

Mind the gaps

What information is missing? That was a question that the EPAA asked Jill Craig from The Centre to answer. Her findings, after a structured process whereby stakeholders were surveyed twice, the second time with the EPAA's assessment of their initial responses and proposals for progress, were clear.

First, the problem is with the quality rather than the quantity of information available. Here the crucial gaps are in knowing what regulators want, in access to full and accurate testing data, in information about validation status (and the process of validation), and in information on progress in the private sector on alternative methods.

Second, the information as it is currently available is poorly presented and organised. Stakeholders want to be able to access information on two levels: basic overviews in lay terms; and links and leads to more scientific and detailed information.

Third, Craig pinpointed a definite need for more emphasis on facilitating and organising dialogue. "There is too much emphasis on information and not enough on interpretation of that information." A major obstacle is that there are no mechanisms for feedback between regulators on the one hand and developers and users on the other. The result is mutual ignorance: the regulators complained that they don't know what is going on, said Craig, while the test developers say they are not told what information to provide.

Fourth, and perhaps surprisingly, Craig found no major differences of opinion between the stakeholder groups. Instead, she found different starting points: policymakers and regulators want more communication and exchange of information; educators, method developers, users – in short, scientists – are more interested in access to quality information, especially peer-reviewed information. Armed with these findings, the EPAA Dissemination Taskforce came up with three possible solutions:

– A proactive push mechanism to address the lack of access to quality information;
– EPAA-sponsored structured dialogue to address the problems of knowing what regulators want;
– EPAA awards to encourage new young scientists into the 3Rs area.

It was the first of these three ideas that attracted the most discussion, which eventually consolidated around the concept of the 3Rs marketplace. Could a body like the EPAA create a marketplace for ideas, so that people developing new approaches could go there and meet like-minded people? Since

the EPAA sits between industry and the public, and is linked with industry and the regulators, it should be an ideal body to act as an "honest broker".

For the coming generation of scientists that link with the regulators could be crucial. Nynke Kramer from the Institute for Risk Assessment Sciences, the Netherlands, spoke up for that generation: "As young scientists we don't really know what regulators want. We know what we can do, but it would be really nice if the EPAA comes in as a broker – but it must be a proactive broker," she said.

If the conference had a leitmotif – apart from dissemination – it would be the well-known question of relations with regulators: what do they want, how can others talk to them, how can they be convinced to take up new ideas? How weak can a dataset be before the regulatory authorities reject it?

However, it's not all one-sided. Craig's surveys for the EPAA by The Centre looked at a mix of regulators. The story they told was that they go looking for the information – in journals, for example – but that in general "only industry" ever sends information in to them.

Engagement with regulators will be achieved by "an intricate learning" process, said Simon Webb from Procter & Gamble. It is all the more necessary, he thought, since regulators are always going to want freedom to consider things on a case-by-case basis. Uncertainty about what regulators want is "not a dissemination problem, but a relationship one", he said.

Conclusions of the workshop

The first conclusion to be distilled from the discussion is that the workshop agreed, in Botham's words, "that it is worth trying to excite the EPAA and others in the idea of the EPAA providing an honest broker service, which we would call a marketplace."

The second conclusion is that progress will only come by doing something concrete, even if small. Botham called for "small-scale experiments, a few things next year", where the EPAA can test the water and see how well the experiments have gone.

Thirdly, dialogue with regulators must continue, in various forms. "We should ask them not just what information they want pushed to them, but also ask, in confidence, what they see as their information gaps."

The full report of the workshop is available on the EPAA website (www.epaa.eu.com).

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Animal suffering and distress – what are the limits of ethical defensibility?

Bad Boll, Germany, 5th-7th March 2010

The introductory lecture at the Protestant Academy Bad Boll by **Peter Kunzmann**, professor of ethics in Jena, dealt with the difference between our treatment of animals held as pets or for experimental purposes, e.g. rabbits. The fact that this ambivalence is gaining recognition and has elicited protest is the consequence of an improvement in ethical valued put on animals by society. Associated contradictions may be found both in the Austrian and German Animal Protection Laws. In the lecturer's opinion, this ambivalence follows from different types of animal-human relationships and may differ between cultures. Kunzmann criticised the categorisation of animals into higher and lower orders and the related special status of primates. He suggested that animal protection should be approached from the animal's perspective and that the problem lies less in unfair but rather in inadequate treatment, e.g. the instrumentalisation of animals.

The Swiss jurist **Gieri Bolliger** from the *Stiftung für das Tier im Recht* showed, using dehorning of cattle as an example, how ethical defensibility must be determined according to §1 of the German Animal Protection Law. The procedure must be justified and commensurability must be demonstrated. The Law requires in some but not all areas that expected benefits must outweigh distress caused. Commensurability requires that the procedure must be adequate and necessary to reach the legitimate purpose. In the example, although dehorning is adequate to reduce the risk of injury for animal and handler, this goal may also be reached by changing the stable design. This result argues against dehorning on ethical grounds although it is still commonly practiced.

Thomas Richter, ethologist at Nürtingen-Geislingen University, discussed whether animal welfare can be evaluated using animal welfare indices. In his opinion, animal welfare depends on a positive mental state of the animal. Neither animal welfare indices referring to the animal's housing, nor the relationship between the handler and the animal or physiological parameters, such as heart rate and stereotypy, are suitable

to assess the animal's mental state. Based on this, allowing an animal to choose between different options is a laborious but exact method to ensure animal welfare.

Brigitte Rusche, *Akademie für Tierschutz in Neubiberg*, explained the general legal constraints and the approach to conflicts of interest regarding animal experiments. German Basic Law (§90 BGB) recognises the value of animals since 1990. However, the clause requiring justification for subjecting animals to pain and distress is too general and must be defined. It should be considered whether bans on performing animal experiments for certain aims should be extended, e.g. to include experiments on vertebrates or severe experiments. It should further be questioned whether the instruments for the ethical evaluation of animal experiments are effective. The different requirements set on killing animals allows them to be subjected to distress for different reasons. Housing conditions are only specified in by-laws for some animals. On the other hand, handling animals requires a permit in some areas, e.g. circuses or animal shelters. It is unclear whether these few concrete prohibitions and unspecific general requirements still reflect the social consensus.

Next to the animal protection check-up (*Tierschutz-TÜV*) mentioned in the Animal Protection Law, an animal husbandry check-up, an animal protection lawyer, an animal ombudsman (like in Austria) or a federal animal protection agent (like in the Federal State of Hessen) and a collective action were proposed.

Four work groups discussed distress caused to animals kept and handled as pets, livestock, wild animals in human care and experimental animals, asking what is ethically defensible and which measures can be taken to ensure ethical treatment of the animals. The results were presented and discussed in a final plenary session. These shall be condensed as a Bad Boll Appeal.

The group on experimental animals reached the consensus that severe animal experiments in education and in basic research should be banned. An animal's ability to suffer was considered a useful basis to decide which species may be used for experiments. No agreement was reached on whether and which species should be excluded from use as experimental animals. It was suggested that ethical evaluation should be based on quantification of the experimental goals with regard to applicability and probability of success, coupled to a time horizon. A retrospective analysis of animal experiments should be submitted to allow a cost-benefit analysis.

It should be ensured that persons and instruments involved in the authorisation procedure have sufficient time to deal with the numerous and lengthy applications. More personnel with suitable qualifications, a catalogue of criteria for the ethical assessment and external consultation are necessary. The Animal Protection Law should require that the animal welfare officer is independent, engaged full-time in this capacity and able to lodge complaints. The §15-commission, of which the animal welfare officer should be a member, must be independent; this would be promoted by an animal protection ombudsman. It was further discussed how the ethical defensibility can be determined and whether animal experiments for luxury items or self-inflicted health problems, such as smoking, should be banned. It was agreed that regulatory animal experiments should at least be subject to a modified authorisation procedure evaluating their necessity. Breeding and killing of animals are not subject to sufficient regulations to allow the evaluation of ethical defensibility. The work group's results were affirmed by the audience.

A resolution on voting on the EU Directive for the protection of animals used for experimental and other scientific purposes was proposed by **Christoph Maisack**. This demands that the Federal Government ensures that the following improvements, which were already part of the proposal for the revision of the Directive published on 5th November 2008 by the European Commission, are indeed included in the revised Directive: provision on authorisation of all procedures involving live vertebrates, cephalopods or decapods; ethical evaluation by the competent authority as an essential requirement for authorisation; obligatory consultation of independent third parties in the evaluation; no experiments on live animals as soon as scientifically satisfactory alternative methods are available; expedited acceptance and approval procedure for alternative methods for regulatory testing; invariable ban on procedures involving severe pain, distress and suffering anticipated to be of longer duration; unconditional enforcement of the housing and care requirements stipulated in Annex A; obligatory admission procedures for all persons wanting to take part in procedures on live vertebrates, cephalopods or decapods; stipulation that at least half of the official controls in institutions breeding, distributing and using animals be unannounced; it is considered especially important that a special article – pursuant to the subsidiarity principle (Art. 5 of the EU treaty) and the proposal made by the European Parliament on 4th and 5th May 2009 – clearly states that the Member States are not prevented from passing and implementing stricter regulations to improve animal welfare and protect animals used for scientific purposes even after the Directive enters into force. The resolution gained a very broad support of the audience.

The meeting initiated varied fruitful discussions, although it was often difficult to find a consensus. Despite the aim of the meeting being to determine the limits of suffering caused to animals that can be ethically defensible, a number of participants held the view that animals may under no circumstances be subjected to suffering. It was suggested that the next meeting be held on the animal's dignity.

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