



# The Center for Alternatives to Animal Testing – Europe (CAAT-EU): a Transatlantic Bridge for the Paradigm Shift in Toxicology

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## Summary

The Center for Alternatives to Animal Testing – Europe (CAAT-EU) was founded based a collaboration between the Johns Hopkins Bloomberg School of Public Health and the University of Konstanz. CAAT-EU, housed at the University of Konstanz, will coordinate transatlantic activities to promote humane science in research and education, and participate, as partner or coordinator, in publicly and privately funded European projects. Thomas Hartung will serve as program liaison representing Johns Hopkins University and Marcel Leist as the University of Konstanz liaison.

CAAT-EU aims to:

- Set up transatlantic consortia for international research projects on alternative methods
- Establish a CAAT Europe faculty and advisory board composed of sponsor representatives and prominent academics from Europe
- Participate in the Transatlantic Think Tank for Toxicology (t<sup>4</sup>) devoted to conceptual work for the paradigm shift in toxicology
- Coordinate a series of information days in Europe on relevant developments in the US, similar to the 2009 series CAAT held in the US on EU issues (one on the 7<sup>th</sup> Amendment to the EU Cosmetics Directive and one on EU and US chemical regulation)
- Support ALTEX as the official journal of CAAT and CAAT-EU
- Develop strategic projects with sponsors to promote humane science and new toxicology, especially with CAAT faculty members
- Develop a joint education program between Johns Hopkins and the University of Konstanz, such as e-courses and the existing Humane Science Certificate program developed by CAAT, a student exchange program, and collaboration with the International Graduate School “Cell-based Characterization of De- and Regeneration” in Konstanz

Keywords: 3Rs, Tox-21c, dissemination, science strategy, international harmonization

## 1 Introduction

W. M. S. Russell and R. L. Burch introduced *The Principles of Humane Experimental Technique* (Russell and Burch, 1959), defining the 3Rs – replacement, reduction, and refinement – as the key strategies for humane research. Russell and Burch’s work has led to a continually evolving search for non-animal alternative methods. In Europe in particular, this has resulted in funding programs and a horizontal laboratory animal welfare legislation. In addition, legislation specific to industrial sector chemicals and cosmetics has become the driving force for a paradigm shift in toxicology. In fact, the 7<sup>th</sup> Amendment to the Cosmetics Directive has become an engine of change, due to the unprecedented commitment of the cosmetics and consum-

er product industries to meet its challenges (Hartung, 2008c). REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals), a recent attempt to improve consumer protection, is unparalleled in size. REACH is the European Union’s program to evaluate the safety of at least 30,000 synthetic chemicals (Rovida and Hartung, 2009) that are already in use (Hartung, 2010b).

More recently, in the US, an exciting discussion has begun. Generally referred to as Toxicology for the 21<sup>st</sup> century (Tox-21c), this approach derives from a report published by the National Research Council /National Academy of Sciences in 2007 (NRC, 2007). It is prompted less by animal welfare considerations than by concerns regarding the limited quality and throughput of traditional approaches. Tox-21c embraces the latest tech-



nologies. Today, research into alternative approaches extends to the development of human cell-based high throughput and high-content methods, as well as computational techniques in the field of safety control, exploiting state-of-the-art knowledge of biochemical and genetic changes (Collins et al., 2008; Hartung and Leist, 2008; Leist et al., 2008; Kavlok et al., 2009). However, we are still far from defining reliable test procedures with human-relevant alternative assessment methods (Hartung, 2009a).

The increasing interest in the field of alternatives has led to the establishment of national, international, governmental, and non-governmental institutions, programs and competence centers, which are committed exclusively or in part to the issue of alternatives to animal experiments. These include the Organisation for Economic Co-operation and Development (OECD), Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), the European Centre for the Validation of Alternative Methods (ECVAM), FRAME (Fund for the Replacement of Animals in Medical Experiments), and others.

The Johns Hopkins Center for Alternatives to Animal Testing (CAAT) is a prominent US institution that has been promoting 3Rs research and human-relevant safety testing for almost three decades (Zurlo and Goldberg, 1996; Goldberg, 2008; Goldberg, 2010). The Center is well known for its effectiveness in the communication, dissemination, and promotion of scientific information about humane science.

The challenge for competence centers dealing with alternative methods is a) to bridge the gaps in communication between the chemical, pharmaceutical, and cosmetic industries and scientists or regulatory authorities, b) to acquire and coordinate scientific projects aimed at developing new, relevant alternative methods and disseminating information on these, and c) to support the implementation of alternative methods by regulatory bodies. Up to now, the different national and supranational competence centers in this field have worked independently of each other at the expense of their impact. In an effort to change this,

CAAT has organized regular meetings of global 3Rs centers at the last three World Congresses on Alternatives and has developed a joint 3Rs and Alternatives Organizations website ([http://caat.jhsph.edu/international\\_alternatives](http://caat.jhsph.edu/international_alternatives)).

The establishment of CAAT-Europe (CAAT-EU) will bring together a number of activities in the field of alternatives to animal experiments and novel approaches in toxicology at the University of Konstanz and combine them strategically with the activities of CAAT at Johns Hopkins University in Baltimore. The core of this partnership is formed by the respective chairs for alternative approaches in Konstanz and Baltimore, both endowed by the Doerenkamp-Zbinden Foundation (<http://www.doerenkamp.ch/en/>) (Wendel, 2002; Leist, 2006). This transatlantic partnership will enable coordinated activities aimed at promoting research and instruction in humane science (Hartung et al., 2009), developing strategic partnerships with stakeholder organizations, and raising funds from industrial and private sponsors, as well as participating in and/or coordinating EU-funded projects.

## 2 CAAT-US: the Johns Hopkins Center for Alternatives to Animal Testing, Johns Hopkins University, Bloomberg School of Public Health (Baltimore, USA)

Henry Spira (1927-1998) is widely regarded as one of the most effective animal rights activists of the 20th century (Singer, 1998). Spira is credited with formulating the idea of “reintegrative shaming,” a technique the animal protection movement uses to convince opponents to change and encourages working with them, rather than rejecting and vilifying them. Working with Animal Rights International, a group he founded in 1974, Spira is particularly remembered for his 1980 full-page advertisement in *The New York Times*. This famous ad, featuring a rabbit with sticking plaster over the eyes, asked, “How many rabbits does Revlon blind for beauty’s sake?” The day the ad appeared, Spira,

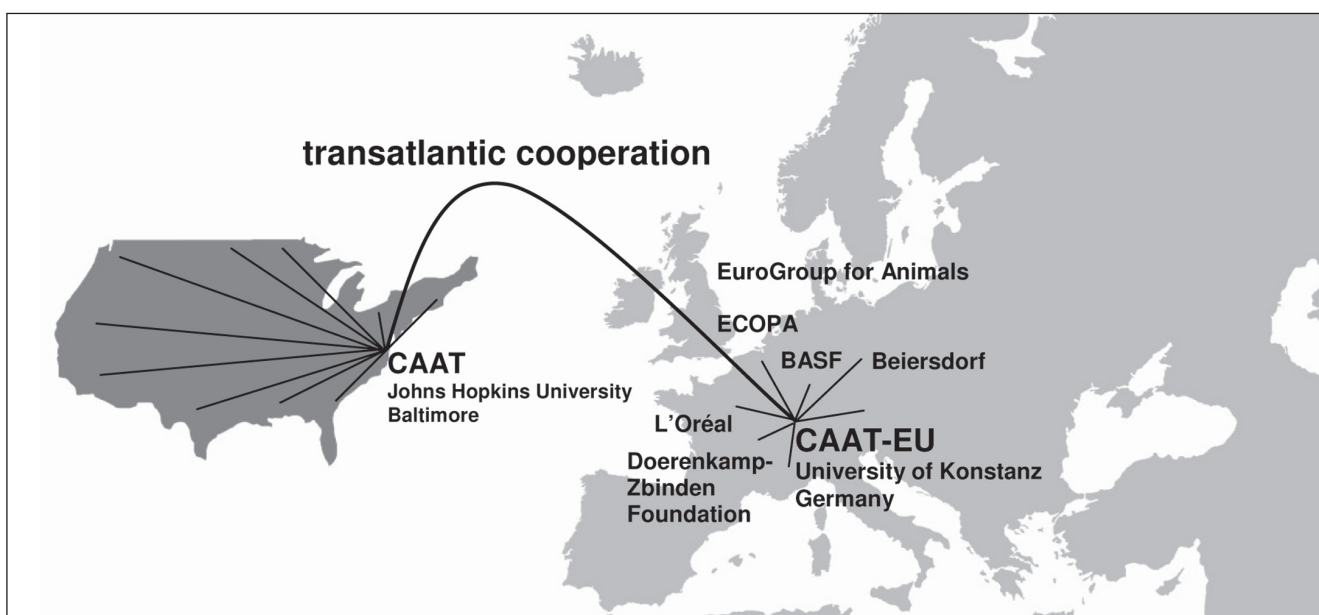


Fig. 1: Scheme of the current CAAT-EU sponsor and collaborator network

dressed in a bunny costume, paraded with a few hundred protesters in front of Revlon's headquarters in New York. Within a year, Revlon had donated \$ 750,000 to a fund to investigate alternatives to animal testing at Rockefeller University. The US Cosmetic, Toiletry, & Fragrance Association (CTFA, now known as PCPC) then collected substantial donations from Avon, Bristol Meyers, Estée Lauder, Max Factor, Chanel, and Mary Kay Cosmetics. These funds led to the creation of the Center for Alternatives to Animal Testing (<http://caat.jhsph.edu/>) at the Johns Hopkins University in Baltimore, headed by Alan Goldberg for 27 years. A wide variety of industries, foundations, and partner organizations have joined the program over the years. CAAT is now directed by Thomas Hartung, the former (2002-2008) Head of the European Centre for the Validation of Alternative Methods (ECVAM, <http://ecvam.jrc.ec.europa.eu/>).

As one of the first competence centers in the field of 3Rs research, CAAT has been a most effective promoter of human-relevant methodology and the 3Rs principles since 1981. Today CAAT enjoys broad support from various industries and foundations (Tab. 1). The advisory board of CAAT consists of representatives from the scientific community, sponsoring industries, regulatory authorities, and animal welfare organizations. This stakeholder representation, unique in the US, has facilitated communication and the flow of information, which are essential for the implementation of innovative and relevant alternative test methods.

As a scientific and academic center, one of CAAT's most effective and influential roles is to stimulate and fund the development of alternative methods. Since its inauguration, CAAT has funded more than ten scientific projects per year, injecting more than \$ 6 million into research on alternatives. Here, the unique composition of the advisory board makes it possible to explore required and relevant alternative methods based on actual demands. CAAT also offers periodic workshops that are highly respected and draw attendees from around the world.

The mission of CAAT also includes communication and exchange between scientists and institutions on alternative methods. The World Congress on Alternatives & Animal Use in the Life Sciences, conceived and organized by CAAT in 1992, is the largest platform for the exchange of information and updates in the field. The World Congress regularly draws close to 1,000 scientists, regulatory authorities, animal welfare advocates, students, and other interested participants from a variety of disciplines.

From the outset, CAAT has been a major force in the dissemination of information about the 3Rs. CAAT's internet portal, Altweb (<http://altweb.jhsph.edu/>), is a pivotal access source for international news and information about alternative methods. Altweb attracts more than 500 visitors per day, illustrating both great public interest in the field of alternative methods and also the significant role CAAT plays in the flow of information.

As of 2009, CAAT also serves as the US editorial office of the scientific journal ALTEX. Now entirely in English and available at reduced rates for members of select alternatives organizations, ALTEX is becoming one of the leading international journals in its field. Most recent additions are regular "news corners" for specific organizations. These include ICCVAM/NICEATM (The Interagency Coordinating Committee on the Validation of Alternative Methods and the National Toxicology Program Interagency

**Tab. 1: Companies and foundations supporting CAAT and/or CAAT-EU**

- 3M\*
- Abbott Laboratories
- Alberto-Culver Company\*
- Allergan
- Alternatives Research and Development Foundation
- American Chemical Council
- Avon
- BASF (CAAT-EU)\*
- Beiersdorf (CAAT-EU)\*
- Bernice Barbour Foundation Inc.\*
- Bristol-Myers Squibb
- Charles River Foundation
- Clorox Company
- The Coca-Cola Company\*
- Dial Corporation
- Doerenkamp-Zbinden Foundation (CAAT-US and CAAT-EU)\*
- ExxonMobil Biomedical Science, Inc.\*
- GlaxoSmithKline
- Humane Society of the US
- Johnson & Johnson\*
- Kimberly-Clark
- L'Oréal (CAAT-EU)
- Lucille Ellis Simon Foundation
- Merck
- PepsiCo\*
- Pfizer\*
- Procter & Gamble Company\*
- Research Institute for Fragrance
- Materials (RIFM)
- Shell Oil Company\*

\*sponsors, i.e. > 60.000 \$/€

Center for the Evaluation of Alternative Toxicological Methods), IIVS (Institute for In Vitro Sciences, Inc., Gaithersburg, <http://www.iivs.org/>), and ECOPA (European Consensus Platform for Alternatives, <http://www.ecopa.eu/>), making ALTEX a primary information source for alternative approaches.

CAAT's efforts include close collaboration with legislators to explore the legal changes necessary to bring about the implementation of alternative innovations, e.g. the concept of Tox-21c. CAAT's impact in the field is substantial, and for nearly three decades, the Center has been a key player in many activities and meetings of the US government concerning safety testing and alternative methods.

The establishment of the Transatlantic Think Tank for Toxicology (t<sup>4</sup>), with partners in Utrecht (Bas Blaauboer) and Konstanz (Marcel Leist), enables conceptual work to be developed for the paradigm shift in toxicology without the pressures of regulating or being regulated. For this purpose, t<sup>4</sup> organizes workshops and stimulates analyses and studies for reporting in ALTEX. These include state-of-the-art reviews of methodologies and cost/benefit analyses, as well as economical, ethical, and philosophical analyses. Systematic reviews translating



methods of evidence-based medicine to toxicology are of particular interest. The Chair for Evidence-based Toxicology aims to promote this concept (Hoffmann and Hartung, 2005, 2006; Griesinger et al., 2009; Hartung, 2009b) and to foster links with the US Cochrane Center at Johns Hopkins. A sabbatical program is in preparation, which will allow colleagues to join the Chair for a couple of months to work on a dedicated project.

CAAT's long-standing commitment to developmental neurotoxicity (DNT), as evidenced by the organization of TestSmart workshops in 2005 and 2008 and a joint workshop with ECVAM in 2005, has enabled the establishment of research laboratories addressing DNT. Organotypic cell cultures, human stem cell models, mass-spectrum based metabolomics, and genomics are used to identify pathways of toxicity. This work builds upon earlier studies conducted at ECVAM (van Vliet et al., 2007, 2008; Hogberg et al., 2009a,b) and will be continued at CAAT by Erwin van Vliet and Helena Hogberg, who joined the CAAT team as post-docs.

The CAAT team includes:

- Thomas Hartung, Director of CAAT, Co-Director of CAAT-EU, Professor and Endowed Chair (Doerenkamp-Zbinden Foundation) for Evidence-based Toxicology, Bloomberg School of Public Health, Johns Hopkins University. He holds a diploma in biochemistry, a PhD from Konstanz (Biochemical Pharmacology) and an MD from Tübingen (Toxicology). From 1996-2002 he was CEO with Albrecht Wendel of the Steinbeis Technology Transfer Center for In Vitro Pharmacology and Toxicology (InPuT). In 2003, he became honorary full professor for pharmacology and toxicology at the University of Konstanz. From 2002 to 2008, he was Head of ECVAM (Joint Research Centre, JRC, Italy). He has authored more than 340 publications and participated in more than 20 EU projects. He is Vice-President of EUSAAT and board member of ECOPA.
- Alan Goldberg, PhD, Founding Director of CAAT (1981-2008) and Professor, Chairman of the Board of CAAT
- Assoc. Professor Paul Locke, JD, DrPH, Deputy Director CAAT policy program
- Dr. Joanne Zurlo, Deputy Director CAAT science strategy program
- Ruth Brady, Carol Howard, Michael Hughes, Betsy Merrill, Liza Mohamed, Marilyn Principe, CAAT staff
- CAAT faculty, a number of professors associated with CAAT and serving on the Board and various projects, including Drs. Jim Yager (JHU-SPH), Mike Trush (JHU-SPH), Joe Bressler (Kennedy-Krieger Institute, Baltimore), Pamela Lein (UC Davis), Gihan Tennakoon (Children's Hospital of Philadelphia), Bernard Robaire (McGill University, Montreal), Sid Green (Howard University, Washington DC), and Wally Hayes (Harvard).

### 3 The unique biomedical competence at the University of Konstanz

The University of Konstanz (<http://www.uni-konstanz.de>) is one of the nine German excellence universities and has about 11,000

students. It has a strong tradition in *in vitro* pharmacology and toxicology, and established Europe's first chair for In Vitro Toxicology and Biomedicine. The University of Konstanz has a biomedical focus – unique in Germany – in the Department of Biology, which recently led to the installation of “Disease Biology” as a new focal area within the Biological Sciences masters program. However, this reflects only the most recent of two decades of developments in biochemical pharmacology and molecular toxicology, including the development of special lecture series, several graduate schools, and research groups financed by the German Research Council, and an innovative concept of combined animal housing and alternative method development under one roof. In this context, alternative methods have been a focus of the University for many years with:

- Marcel Leist, PhD, Co-Director of CAAT-EU, Doerenkamp-Zbinden Endowed Professor and Chair for In Vitro Toxicology and Biomedicine. His work focuses on neurotoxicity, including the use of human stem cells (Leist et al. 2008c). He holds an MSc in toxicology and a PhD in biochemical pharmacology. He was assistant/associate professor of toxicology at the University of Konstanz from 1995-2000. Until 2006, he worked as Head of Department on a broad range of toxicological and pharmacological projects within an industrial setting at H. Lundbeck A/S (Copenhagen, DK). He has published more than 120 peer-reviewed papers.
- Alexander Bürkle, MD, Professor and Chair of Molecular Toxicology, whose focus is on genetic toxicology, poly(ADP-ribosylation), neurotoxicology, and prion diseases. Among others, the group established an improved, automated version of the fluorescence-detected alkaline DNA unwinding (FADU) assay to quantify formation and repair of DNA strand breaks in living cells.
- Daniel Dietrich, PhD, Chair of Environmental Toxicology at the University of Konstanz, with adjunct professorships at the Institute of Technology (ETH) in Zurich, Switzerland, and the University of Pittsburgh, School of Public Health, Pittsburgh, USA. Dr. Dietrich has been on several task forces at ECVAM, is an expert for the US Environmental Protection Agency (EPA), presently co-chair of the Validation Management Group “Non-Animal Testing” of the OECD, and a major partner in several FP7 EU-funded projects aimed at better use and predictivity of high-throughput techniques (CHEMSCREEN) as well as improved safety sciences education in the pharmaceutical industry (IMI-JU SafeSciMET).
- Thomas Hartung, MD, PhD, honorary full professor of pharmacology and toxicology, in parallel with his position as Director of CAAT at JHU.
- Albrecht Wendel, PhD, Professor and Chair emeritus of Biochemical Pharmacology, Presently CEO of the Interfaculty Center for Pharmacogenomics and Pharma Research (ICEPHA) at the University of Tübingen, Germany, and formerly CEO of the Steinbeis Technology Transfer Center for In vitro Pharmacology and Toxicology (STZ InPuT) 1996-2008. The center has carried out more than 100 contracts with companies and the public sector in eight countries.
- Franz Gruber, DVM, PhD, acting as hon. assoc. professor, President of the Doerenkamp-Zbinden Foundation, Switzerland;

Editor-in-chief of ALTEX, the 25-year-old journal on alternatives to animal experimentation, edited by the Swiss Society ALTEX Edition and published by Springer. ALTEX is also the official journal of EUSAAT and CAAT.

- Sonja von Aulock, PhD, filling the position of an assoc. professor; *in vitro* pharmacology, toxicology and immunology, including work on the alternative pyrogen test; subeditor of ALTEX.

At the University of Konstanz an alternative pyrogen test was developed (Hartung and Wendel, 1995; Daneshian et al., 2009) and validated (Hoffmann et al., 2005; Schindler et al., 2006, 2009), which was accepted by the European Pharmacopoeia and the US Food and Drug Administration (FDA) in 2009. The test will be marketed by Biotest microbiology unit (hycon@biotest.de). The development of this *in vitro* kit, containing all necessary components, under the name of Pyro-Detect System is in its final stage. First test kits for customer trial are available.

#### 4 Necessity of transatlantic collaboration

For North American and European countries the last decades were characterized by a rapid development of industry, associated economic benefits, and individual comfort. This comfort is largely based on products from the chemical, cosmetic, and pharmaceutical industries, but toxicological data for approximately 86% of the synthetic chemicals in use today are fragmentary or lacking (Hartung, 2009c). It seems obvious that this large quantity of information, so vital to consumer protection, can be gathered most effectively in a joint effort between governments and the scientific community on both sides of the Atlantic.

Although the US and Europe have attained comparable levels of development and, therefore, have the same needs, their emphases on regulation and scientific attention differ in various areas (Hartung and Bottini, 2009). This is especially so for the role of alternative approaches. Where the Europeans started with REACH and the 7<sup>th</sup> Amendment to the Cosmetics Directive, i.e., the characterization of synthetic chemicals and the legal restriction of animal tests, the US National Academy of Sciences, with “Toxicity Testing and Assessment in the 21<sup>st</sup> Century” (Tox-21c), stress the implementation of high-throughput, human-relevant alternative methods in regulatory safety control. These are not developments heading immediately in opposite directions, but their different approaches mean that US companies will have difficulties targeting the European market, and Europeans may be left behind, lacking the potential impact of the Tox-21c in their regulatory toxicology.

As multinational companies are global players and their smaller national providers indirectly depend on the same markets, their struggle through the rampant jungles of national and supranational regulatory affairs are economically counterproductive. Science is borderless; academics contribute to regionally differing safety approaches pending current local political decisions, so any lack of collaboration is also scientifically counterproductive. Most notably, industries as well governments benefit economically and scientifically from harmonization of transatlantic regulations. The not-always-harmonized current state throws a wrench into the economies on both side of the Atlantic. Taken

together, both sides are on a par with regard to their needs and are at a similar stage of industrial and scientific development. Moreover, both the EU and the US have taken on pioneering roles in protecting consumer safety. Unfortunately, the different directions and speeds of development on each side of the Atlantic may constrain both sides, whereas harmonization could lead to synergy. We have seen the tremendous impact of harmonization on OECD and ICH levels on avoiding duplicate animal testing (Bottini et al., 2007). This success may have overshot its goal, however, leading to a high inertia with respect to further changes and making it difficult to further optimize the guidelines, e.g. in adaptation to technical progress.

#### 5 CAAT-EU: Center for Alternatives to Animal Testing – Europe at the University of Konstanz, Germany, the first international academic competence center for alternative approaches

The unique and promising concepts upon which CAAT is founded have served the field of alternative methods and safety control well in the US for nearly three decades. Its concepts and structure will be adapted for the establishment of its European counterpart. CAAT and CAAT-EU are committed to the critical evaluation of *in vivo* (Hartung, 2008), *in vitro* (Hartung, 2007), and *in silico* (Hartung and Hoffmann, 2009) approaches, especially those that follow principles of evidence-based toxicology (Hoffmann and Hartung, 2006) and the Tox-21c movement (Hartung, 2009a,c). CAAT’s efforts – on both sides of the Atlantic – address cosmetics (Hartung, 2008), chemicals (Hartung, 2010), food (Hartung and Koëter, 2008), and pharmaceuticals.

The creation of CAAT-EU was announced at the 7<sup>th</sup> World Congress on Alternatives and Animal Use in the Life Sciences, held in Rome, Italy (August 30 - September 3, 2009). The Memorandum of Understanding between the Johns Hopkins Bloomberg School of Public Health and the University of Konstanz was signed in December 2009, and the first sponsors came onboard immediately: BASF, Beiersdorf, L’Oréal, and the Doerenkamp-Zbinden Foundation.

CAAT-EU at the University of Konstanz will be established in rooms currently used by Professors Leist, Hartung and Bürkle. Dr. Mardas Daneshian will direct its daily activities, with the aid of administrative staff.

The goals and visions of this transatlantic competence center include:

- Establishing a European advisory board consisting of experts from basic science, regulatory agencies, industry, and animal welfare. This synergy will lead to innovative and relevant alternative testing methods and research tools, lending support to the search for realistic decisions on ongoing projects (for example, REACH). The CAAT-EU faculty and board will include sponsor representatives, as well as prominent European academics (including Prof. Dr. Michael Schwarz, Tübingen, Germany; Prof. Dr. Bas Blaauboer, Doerenkamp-Zbinden Professor for Alternative Methods, Utrecht, The Netherlands; Prof. Dr. Walter Pfaller, Medical University of Innsbruck, Austria; and Dr. Joanna Jaworska, P&G, Brussels, Belgium).



- Establishing a broad industrial sponsor base and developing strategic projects with sponsoring industrial partners to promote humane science and new toxicology in projects, especially with CAAT faculty members.
- Setting up and partnering in transatlantic consortia. First examples addressed nanotoxicology and several applications in the call for proposals put forward by the EU and cosmetic industry, making available € 50 million for systemic toxicity alternatives. The focus will be on human-relevant alternative methods making safety control and research more ethically acceptable.
- Setting the course for transatlantic convergence in regulatory toxicology and 3Rs research. CAAT-EU promises a real transatlantic dialogue as a credible academic platform.

Developing joint education programs between Johns Hopkins University and the University of Konstanz that involve additional academic institutions (Hartung et al., 2009), for example the e-courses and certificate programs on humane science developed by CAAT, student exchange, and collaboration in the International Graduate School (International Research Training Group – IRTG 1331 – “Cell-based Characterization of De- and Regeneration”, Konstanz, Germany and Zürich, Switzerland), which is currently applying to the German Research Council (DFG) for an extension.

- Providing a strong academic voice as expert counsel for questions concerning current and developing non-animal safety methods and research tools, as well as supporting further developments in these fields in different countries.
- Participating in programs, projects, congresses, and workshops worldwide that deal with the issues of safety control and in vitro test methods. The center will participate in the Transatlantic Think Tank for Toxicology (t4), devoted to conceptual work for the paradigm shift in toxicology. The center will offer a series of information days in Europe on relevant developments from the US, similar to the programs held on developments in Europe by CAAT in the US. The first information day, planned for June/July 2010, will provide an overview of US activities toward “Toxicology for the 21st century”. A workshop on education in alternative approaches is planned for October 2010.
- Supporting ALTEX as the official journal of CAAT and CAAT-EU, and disseminating information on achievements in the field of alternative testing via Altweb (<http://altweb.jhsph.edu>).
- Making industrial partners aware of the evident synergistic benefit of transatlantic CAAT boards: direct interaction and collaboration with regulatory authorities, access to sound, substantive scientific knowledge, and firsthand updates on scientific and regulatory developments.
- Steering the conceptual draft for a global human toxicology project (Hartung, 2010a; Seidle and Stephens, 2009).

CAAT-EU has initiated the first strategic collaborations with ECOPA (<http://www.ecopa.eu/>) and EuroGroup for Animals (<http://www.eurogroupforanimals.org/>), which are represented on the CAAT-EU board. ECOPA is a quadripartite NGO-organization that promotes the 3Rs in Europe. It brings together national consensus platforms on alternative methods, with

“consensus” meaning that the major stakeholders, i.e. animal welfare, industry, academia, and governmental institutions, are equally represented. ECOPA is active in science, education, and ethical issues with respect to 3Rs alternatives with 16 national platforms. EuroGroup for Animals – the leading animal welfare organization of the EU – has represented its more than forty member organizations for more than 25 years. The group provides advice and expertise on animal welfare to the European institutions – the Council of Ministers, the European Parliament, and the European Commission.

## 6 Additional remarks

Due to the hesitant awakening and high inertia of regulatory toxicology, academics still have to struggle with rigidities in this field, and huge numbers of animals are used in tests that may not be relevant for increasing safety of humans. Here the paradigm shift in toxicology leads to a change in the underlying theoretical concept of safety sciences. The term “human-relevant method” is often misunderstood as just a technical improvement of methods. This human-centric idea tends to ignore the value of the animal. Indeed, the community probably runs the risk of forgetting that education toward the involvement of non-animal methods is pivotal for installation of ethical values into the scientific community.

At this point we wish to stress that CAAT-EU advocates and welcomes the paradigm shift in toxicology but also defines the “ethical idea of 3Rs” and “human-relevant methods” as two sides of the same coin.

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