Food for Thought ... on Education in Alternative Methods in Toxicology

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If you cannot change things, educate those who will. Or, as George Bernard Shaw put it more cynically: "He who can, does. He who cannot, teaches." The three authors of this *Food for thought* article have one thing in common: due to the generous support of the Doerenkamp-Zbinden Foundation (http://www.doerenkamp.ch/en/), we each hold an endowed chair for alternative methods in toxicology, one at each of three prominent universities. Such chairs, established within the faculties of public health, veterinary medicine, and biology, respectively, are the basis for the development of new curricula (Wendel, 2002; Spielmann, 2002; Leist, 2006). In the meantime, two more chairs have been established by the DZ Foundation in Lausanne, Switzerland, and Tiruchirappalli, India, but these do not focus on the field of toxicology. Many subjects considered in this article might be translated to areas other than toxicology, but this would require a case-by-case assessment.

The authors have also joined forces with Alan Goldberg of Johns Hopkins University, who established the first academic center for alternative methods 28 years ago (Goldberg, 2009). Together these four "ambassadors" form the Transatlantic Think Tank for Toxicology (t^4) (Fig. 1) aimed at developing concepts for the paradigm shift in toxicology and creating a network for the implementation of the US National Research Council vision (NRC, 2007) of a toxicology for the 21st century (Tox-21c) (Hartung, 2009a). Here, aspects of teaching alternative approaches and possible synergies shall be explored.

We have elaborated, in this series of articles and related publications, on the need for a paradigm shift in toxicology (Hartung and Leist, 2008) and on the means to create a new approach, i.e. *in vitro* (Hartung, 2007a), *in vivo* (Hartung, 2008a) and *in silico* (Hartung and Hoffmann, 2009) approaches and their validation (Hartung, 2007b). An assessment of the value of 3Rs approaches has been presented (Leist et al., 2008a), as well as opportunities for an evidence-based toxicology (Hartung, 2009b). The case for change has also been made on the basis of economic developments (Bottini et al., 2007; Bottini and Hartung, 2009). Some specifics of the areas of cosmetics (Hartung, 2008b) and food (Hartung and Koëter, 2008) have been addressed. A series of articles outside this *Food for thought* series complements the picture, e.g., mapping the implementation of Tox-21c (Hartung, 2009c), discussing regulatory usefulness of new approaches (Hartung and Daston, 2009), opportunities of stem cells (Leist et al., 2008b), the revolutionary character of the ongoing change (Hartung, 2008c), and the needs of REACH (Rovida and Hartung, 2009; Hartung and Rovida, 2009). But this will not happen and cannot be implemented without changes in mindset and the efforts of people with the right skill sets to implement it. Education is the means to achieve these goals. The Swiss cognitive psychologist Jean Piaget said: "The principal goal of education is to create men who are capable of doing new things, not simply of repeating what other generations have done."

A couple of questions come up immediately: Do we need education on alternatives or on a new toxicology? Do we need to create new courses and curricula or modify the current ones? Whom do we need to target, the next generation (students), current practitioners (post-graduate level), senior management (decision makers), or all of them? Which areas of study and work environments should be targeted: biology, chemistry, medicine, veterinary medicine, other life sciences, risk assessors, lawyers, policy makers, regulators, etc.? How can we achieve coverage of large numbers of target audiences? How to network and synergize in a situation of diaspora, i.e. where the different offers and competence centers are widely dispersed? Is "alternative methods" the right catch phrase or should we label it "new toxicology?" Are we teaching alternatives or are we teaching with

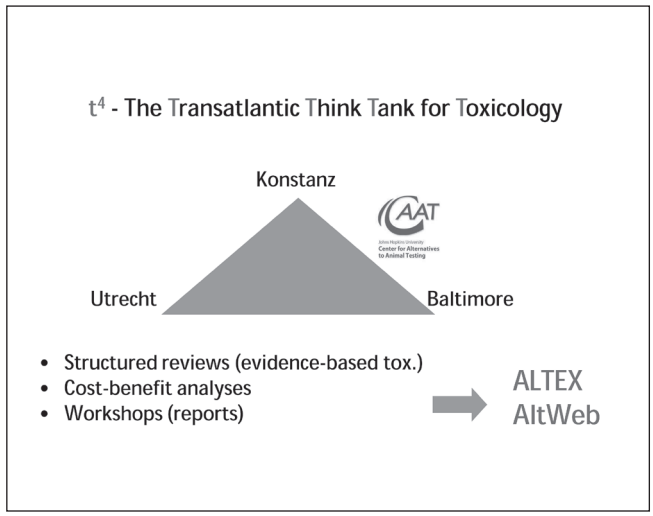

Fig. 1: t^4 – The Transatlantic Think Tank for Toxicology

alternatives? Which modern communication tools accelerate and optimize education? Should the training of people to be licensed to do animal experiments be obligatory, as is happening in The Netherlands?

The authors hold the first chairs for alternative methods in toxicology established by the Doerenkamp-Zbinden Foundation. In addition to their research and translational contributions, they are involved in teaching novel, humane approaches to the science of risk assessment. This article is less a position paper than an attempt to define challenges to further education toward a new toxicology.

Consideration 1: Alternative is a mindset, not a technology or a scope

The phrase "alternative methods" has been the terminology applied to 3Rs approaches (replacement, reduction, and refinement of animal experiments) since the 1970s. At the time, "alternative" was commonly used as a description of anti-establishment or activist types, typically environmentalists. It is quite remarkable in this historical context that there is currently (despite considerable similarity in anti-establishment approach) a substantial divide between environmental and animal welfare activists, i.e. many environmentalist groups favor animal testing to generate data on hazards and risks of environmental chemicals. More recent discussions of current approaches, with a focus on quality of data and throughput capabilities, are bringing on board more stakeholders with a longer perspective.

The term "alternative" has created tremendous problems because of the "anti-establishment" associations. When, for example, the German National Centre for Documentation and Evaluation of Alternatives to Animal Experiments (ZEBET, http://www.bfr.bund.de/cd/1591) was created, the word *Alternativmethoden* was avoided using *Ersatz- und Ergänzungsmethoden* (replacement and complementary methods) instead. This might be surprising, as science should be, at its best, moving forward and challenging the current, the established, and the state of the art. Risk assessment, however, is also an applied discipline with political and economic aspects and constraints. The goal of alternatives is not to be "anti-establishment," but to develop approaches that are both more effective and more humane.

Alternative approaches cannot be defined by any single technology – science that does not perceive itself as alternative uses the very same methods as those deemed "alternative," often developing methods that only later find their way into alternative use. For example, *in vitro* methods are rarely developed with the goal of replacing animal experimentation, and they are broadly used for the study of physiology or effects of agents without directly substituting for an animal experiment.

Alternative methods are often defined by the intention to replace, reduce, or refine animal use, and these are certainly key components. However, these should always be the goals for any ethically thinking scientist. We should be aware that they do not necessarily achieve the goal of reducing animal numbers if, for example, they just increase throughput of substances, move more substances from screening to animal models, or if positive results trigger increased testing demands. Very often, alternative methods represent enabling technologies, allowing us to do things that were not possible with the traditional animal test!

In a more accurate sense, alternative methods refer to new approaches in risk assessment in the regulatory arena. In this domain, established tests require formal validation of alternatives before they can be replaced. We should be clear that this is a very small part of all animal use: roughly 10% of animal use is in the field of toxicology and alternatives make up a small fraction of toxicological testing. Does this require educating specialists in fields other than toxicology? We might argue in favor of education in alternatives serving as a "lighthouse." We might argue that every opportunity for ethical discussions will broadly benefit the student. This means that students who later choose other areas of work will benefit from more advanced examples of humane experimental technique and later consider them in their own work.

We can, however, go somewhat further. Alternative methods are pioneering a critical approach to method development. This involves defined measures for quality assurance and for unbiased evaluation of technologies, from which many areas of science could benefit. More than anywhere else in the life sciences, the reliability and relevance of tools are assessed, a culture of quality assurance has been established, and means and consequences of practical implementation are discussed. It is here, where Good Laboratory Practice (Cooper-Hannan et al., 1999) and Good Cell Culture Practice (Hartung et al., 2002; Coecke et al., 2005) come into play; it is here that international validation bodies are collaborating; and it is here that national coordinators monitor and negotiate the revision of test guidelines. All of these are most valuable for forming a truly scientific mind-set, or "Man's going forward from cocksure ignorance to thoughtful uncertainty" as Kenneth G. Johnson cleverly phrased it.

Teaching of alternative methods, not just a historical account of change in methods, is critical. To be relevant to a larger audience, teaching should embrace quality, relevance, and usefulness, which would enhance many other scientific areas well as aid in developing key performance indicators. It is astonishing how infrequently these fundamental concepts are posed to scientific approaches in research. We tend to use what is at hand and consider it correct when the results suit us and the small number of repetitions do not indicate variability of results. When developing concepts for a Good Cell Culture Practice (Hartung et al., 2002; Coecke et al., 2005) it was essential to understand how many variables of an experiment should be controlled and documented – an approach far from common in academic research. Similarly, the efforts toward validation (to show that a method is reliable and relevant) would suit much of our research, but few are eager to invest the years and hundreds of thousands of euros for each method applied.

For the purpose of teaching the 3Rs, it appears that the term "alternative methods", with its various connotations, is not correctly communicating all of the above-mentioned concepts. Better selling points might be offered by a label such as *new method-critical, evidence-based, pathway-based*, or *systems*

toxicology. However, more important than the given label is the need to teach an alternative approach, not alternative methods. As Goldberg stated (2004), "We must train those who come after us in the principles and practice of humane science."

Consideration 2: The novel approach needs to become part of various curricula and targeted education programs

First of all, the education of toxicologists should be closely examined. For example, when does someone become a toxicologist? Dedicated Master's programs are relatively rare in Europe (Internet research found 11 in Basel, Berlin, Copenhagen, Glasgow, Guildford, Kaiserslautern, Leiden, London, Stockholm, Utrecht, and Vienna), while 28 such programs were found in the US (http://www.universities.com/edu/Masters_degrees_in_Toxicology.html). It is remarkable that most of the European programs seem to be very recent (in part because of the Bologna process, which led to mushrooming of novel master specializations), which might indicate a reaction to the suddenly increased demand for toxicologists, especially for REACH. Once again, specialization comes too late, since positions are being filled now, and will be filled in the near future, by drawing upon neighboring disciplines. This has interesting consequences for methodological background, depth of experience, need for training on the job etc. However, other upcoming programs, like nanotoxicology or endocrine disruptor screening, might sustain the demand; therefore, initiating the education of toxicologists now might not be such a bad idea.

Unfortunately, most students in the life sciences have little exposure to toxicology. A few enter the field via research practice (master or diploma or PhD/MD thesis) or training on the job, but are rarely backed by major systematic education. Some post-graduate and vocational training is offered by toxicological societies and universities, e.g.:

- the American Society of Toxicology, http://www.toxicology.org/ai/ce/ce.asp
- the British Toxicology Society, http://www.thebts.org/index.php?content=gi_train
- Dutch postgraduate education in toxicology, http://www.toxcourses.nl/
- EuroTox, http://www.eurotox.com/pag.asp?ID_pagina=69
- the German Society for Experimental and Clinical Pharmacology and Toxicology (Hesse-Callaway and Greim, 1996), http://www.dgpt-online.de/html/text_fr.htm
- TRISK – European Toxicology Risk Assessment Training Programme, http://www.cascadenet.org/projectweb/4667c4853b2a6/TRISK.html

Alternative methods are part of such curricula at varying levels. Still, it is fair to say that most graduate studies do not include major toxicology curricula and even fewer include emerging novel approaches.

But how important is the knowledge of specific alternative approaches for the future toxicologist? Probably not too much – it will be more important to learn how to find available alternative methods by queries to pertinent databases, such as:

- ECVAM (dbAlm, http://ecvam-dbalm.jrc.ec.europa.eu/)
- ZEBET (AnimAlt-ZEBET, http://www.bfr.bund.de/cd/1508)
- US National Library of Medicine (ALTBib, http://toxnet.nlm.nih.gov/altbib.html)
- UC Davis Center for Animal Alternatives Information (http://lib.ucdavis.edu/dept/animalalternatives)
- Altweb Guide to Searching for Alternatives (http://altweb.jhsph.edu/resources/searchalt/index.html)

Searching for alternatives is still a major problem. At ECVAM, we initiated a project to develop "good practices" for searching databases, which was carried out by ZEBET. The work was completed and will be published soon. With this guidance, it is much easier to make an exhaustive search – important, for example, for animal use committees as well as the proponents of animal tests. The Technical University Dresden and ZEBET (www.go3R.org) have developed further interesting search approaches. This semantic search engine uses the information of the US PubMed but promises more exhaustive and selective recovery of relevant documents.

Thus, every researcher considering animal use or its alternatives should know about how to find, relevant alternatives. But knowing the options is only one step: the researcher must be willing to seriously consider alternatives in the first place. It is always possible to argue that available alternatives are not applicable for a given research problem. Consequently, it is important to understand the limitations of an animal approach. The scarcity of literature on the limitations of animal models is astonishing, as discussed in an earlier *Food for thought* article (Hartung, 2008a). Furthermore, we typically discuss only the advantages of alternative methods. Teaching a method-critical view of alternatives is probably even more important for the (future) toxicologist than teaching specific methods themselves.

It would be as problematic, however, not to point out the shortcomings of the alternative approaches, as discussed for *in vitro* methods (Hartung, 2007a) and *in silico* methods (Hartung and Hoffmann, 2009) in this series of articles. New methods come and go, but the principal limitations of modeling and testing remain. The pace of new technologies coming to the laboratory makes it almost useless to teach any approach, except as an example. The principles of statistically valid experimental design, of documentation, of data analysis and visualization, however, are much longer-lived. It is astonishing that they are little taught in most curricula.

Consideration 3: Teaching with alternatives is different from teaching about alternative methods

Impressive progress has been made in the replacement of animal experiments in education as promoted by organizations like:

- European Resource Centre for Alternatives (EURCA, www.eurca.org)
- International Network for Humane Education (InterNICHE, www.interniche.org; Jukes and Chiuia, 2003)
- The Norwegian Reference Centre for Laboratory Animal Science and Alternatives (NORINA – a Norwegian Inventory of Audiovisuals, http://oslovet.veths.no/fag.

aspx?fag=57&mnu=databases_1)
- The Humane Society Veterinary Medical Association (http://alted.hsvma.org/)
- The UC Davis database (http://www.vetmed.ucdavis.edu/Animal_Alternatives/)

Various articles summarize the methods available and their pros and cons (Van der Valk et al., 1999; Balcombe, 2000; Gruber and Dewhurst, 2004; Martinsen and Jukes, 2005).

Today, very few teaching needs, except for teaching animal experimentation itself, require sentient models. Even to introduce animal experimentation, many steps (such as surgical techniques) can be trained with cadavers or virtual, plastic, or other sorts of non-animal models (Fanua et al., 2001; Schöffl et al., 2008) with very positive acceptance by the students (Silva et al., 2007). Video recordings of the animal test are often substitutes. It is often a matter of costs, knowledge of availability, and pressure by students that such models are introduced into curricula. It has been repeatedly shown, by sound scientific methodology, that such models offer advantages and do not represent limitations to the traditional animal models (Patronek and Rauch, 2007; Knight, 2007a).

We should be clear, however, that this rather limited animal usage (less than 2%, according to European animal use statistics) has little to do with the implementation of a new toxicology – rather, it is avoiding animal use in teaching for students of medicine and veterinary medicine and a few life science courses. Most participants of these courses might never again use animals for their job practice or research.

The content of teaching alternative approaches should be three-fold: (1) alternative methods, (2) alternative thinking about quality assurance, as discussed above, and (3) the limitations of current approaches. The latter will perhaps have the most important impact on animal use, especially in the fields of basic research and agent discovery (which together make up two thirds of all animal use), where classical alternative methods are rare and the central implementation mechanism of validation is often not feasible. Frequently it is overestimation of the quality and predictive value of the animal model that makes us continue to use it. Too often, we neglect the inherent limitations of our models. It was very telling when the article on limitations of animal models was prepared (Hartung, 2008a) for this series of *Food for thought* articles that not a single review article was found in PubMed on the shortcomings of animal tests.

Consideration 4: Teaching of an alternative approach is necessary at many diverse places in many different curricula – thus pointing out the need for new forms of teaching

For now, the number of competence centers for alternative approaches is few, but the audiences are many. Thus, teaching approaches are necessary to address this problem, such as bringing students together from various places for intense learning experiences and exchangeable teaching materials (for example, lecture materials, text books, and e-learning resources). A central depository of teaching materials for alternative methods (see below) could be an interesting first step. There are some textbooks on alternatives (Goldberg, 1993; Gruber and Spielmann, 1996; Salem and Katz, 2003; Hester and Harrison, 2006; Balls, 2009), but we are not aware that they are used in classes. With increasing teaching demands, this might actually become a need; in particular, a textbook that addresses elements of the alternative approach and not just a laundry list of alternative methods. Currently, such a text should take stock of the challenges ahead and not just focus on past successes. E-learning, i.e. Internet and computer-based teaching, is becoming more and more popular. The Johns Hopkins course on humane experimental technique, developed by Alan Goldberg and Paul Locke at CAAT, is such an example. CAAT's academic programs educate students and professionals in the research field about alternatives and humane science, helping them gain a better understanding of the 3Rs and their role in improving the quality of science. The Humane Science and Toxicology Certificate Program is central to CAAT's academic program, with a curriculum consisting of six courses, offered both in the classroom and online, through the Johns Hopkins Bloomberg School of Public Health.

The certificate program (http://commprojects.jhsph.edu/academics/prop.cfm?id=32) is open to anyone with an undergraduate or graduate degree in public health or the biomedical sciences, as well as to students in any degree-granting program at the Johns Hopkins University. In an important step designed to make the Certificate Program easily accessible to wide audience in business, legal, and regulatory communities, CAAT is working to make the Humane Science and Toxicology Certificate Program available entirely online by 2010.

CAAT also offers a free online course: Enhancing Humane Science/Improving Animal Research. This course provides a broad overview of diverse topics in humane science, including experimental design, humane endpoints, environmental enrichment, post-surgical care, pain management, and the impact of stress on the quality of data. The self-paced course consists of 12 audio lectures with accompanying slides, resource lists, and study questions, and is available on the CAAT website (http://caat.jhsph.edu/).

In Switzerland a 3R training and test program may be found on the website (http://3r-training.tierversuch.ch/en/module_3r.html). In 2005, the Swiss Association of Cantonal Veterinarians officially recommended the 3R Module to the authorities for mandatory vocational training.

Consideration 5: The golden "rule" if there are few teachers and many putative students: teach the teacher

Today, very few individuals are actively teaching alternative approaches. Many of the players in the field are anchored in industry, research institutes, the regulatory arena, or NGOs. Thus, they contribute to academic education only via adjunct appointments, if at all. However, not to be underestimated is the continuous research funding for alternative approaches that brings academic groups into the field. In many instances this has led to incorporation of these experiences into the lecturing activities

of the researchers involved. What we need, however, is help in increasing these activities. The lack of training for university teachers in *teaching* is notorious. If it is addressed at all, it is on the general skill level, with offers for the younger colleagues and not necessarily those who most urgently need it but rather those less resistant and who will benefit longest. It is probably unrealistic to aim to train academic instructors how to teach a subject such as the 3Rs. However, when offered as an exchange of experience it might work. We plan to propose such an offer in the near future.

The authors intend to set up, in the context of CAAT, an initiative to bring together teachers interested in 3Rs methods and the paradigm shift in toxicology to support collaboration, exchange of experiences, and teaching materials, with possible collaboration on joint initiatives such as workshops, summer schools, combined e-learning offers, or initiatives to update curricula. One idea is a central depository of teaching materials. This might include sharing slides, pertinent texts, literature, photographs, cases for problem-oriented learning, and the like. We are currently trying to create a network of teachers of alternative approaches and plan for such a depository between the collaborators.

The intended depository, as part of a collaboration between individuals and organizations teaching alternative approaches, is only one step. Another promising approach may be to offer education in the 3Rs for teachers at high and middle school levels. Together with the repository of teaching materials, this promises to get new content implemented into curricula at all levels. It is appealing to start teaching alternatives as part of the scientific education before college and university. However, we are not aware of many opportunities at present for teachers in middle and high schools to explore the topic. CAAT created earlier a series of publications called *CAATalyst* (http://caat.jhsph.edu/publications/caatalyst/index.htm) to introduce the concepts of alternatives to animal testing to middle school students and their teachers. The materials are available in printed format, as well as online.

Another interesting example is a DVD on cell culture methodologies for middle schools, high schools, and universities prepared by the Italian Platform for Alternatives in 2006 (IPAM, http://www.ipamitalia.it).

A most promising target group for training are animal use committees (IACUC) and institutional ethical review boards. These individuals have a key role in influencing the actual use of animals and animal alternatives. Since this group also includes lay people, this might represent a special challenge, compounded by the fact that the target group is dispersed at many institutions. Again, an Internet-based offer might be most promising here.

Consideration 6: Change curricula and export these changes to other areas and regions

Consensus on the integration of new content (especially as mandatory elements for a certain qualification) is certainly the most effective way to implement such new material. Recently, many larger institutions have shown a willingness to include alternative approaches (at least as a fig leaf…) in their education. Curricula on toxicology or animal experimentation often contain alternative methods. However, there is little standardization and exchange of content. One reason, certainly, is that there is no society to standardize and push for the integration into curricula. This might be an objective for organizations like the European Society for Alternatives to Animal Testing (EUSAAT, www.eusaat.org) or European Society for Toxicology in vitro (ESTIV, www.estiv.org). Perhaps their upcoming first joint meeting in Linz in September 2010 represents an opportunity to begin a dialogue on this topic. It might be worthwhile to suggest an EU policy support action to develop such prototypic curricula and promote them to the various societies and institutions for consideration.

Consideration 7: An academic teaching structure is the basis for retaining and recruiting talents

Not only sports organizations, but also music orchestras and professional groups invest considerable resources into the teaching of "new blood." This has not only educational benefits, but plays also an important role in recruitment. Attracting young people to certain careers by offering an appealing teaching program becomes especially important in competitive situations and with demanding recruits. This clearly applies to the field of alternative methods in toxicology or 3Rs teaching as a biomedical topic. In all disciplines of science and technology, talented students are currently in high demand. This group of students, in particular, chooses its career field with care. They must be targeted by making the area of the 3Rs known to them and by offering them inspiring and attractive teaching, e.g. by establishing a comprehensive educational curriculum. The latter activity is intimately linked to incorporation of the 3Rs as a serious academic topic at leading universities, for instance, in the form of dedicated chairs. This also offers a career perspective, and is, therefore, an important factor in the consideration of whether students choose our field of work.

A dedicated academic teaching program also has at least three additional effects on recruitment to the 3Rs discipline. First, once established at a university faculty, parts of the teaching program are naturally exported to neighboring disciplines within the context of various courses. Thus, a general understanding and appreciation of the field spreads broadly among students of various disciplines. The second role deals with interdisciplinary nature of the field. We feel that the full breadth and depth of the 3Rs can only be covered in education by a dedicated academic institution. This does not preclude coverage of many individual aspects, in one way or another, in general courses in toxicology or animal experimentation. To our knowledge, however, this is usually heavily focused on one particular discipline. The full career potential and fascinating aspects of an interdisciplinary, complete and balanced teaching program might draw a broader group of students than those visiting specialized courses within the context of another field. The third aspect is that a fully established academic teaching structure attracts not only students

(vertical recruitment), but also mature scientists who want to advance in the field or enter the field sideways (horizontal recruitment). At the moment, enormous numbers are recruited to positions with a toxicological component within the context of REACH, making it mandatory to provide the horizontal recruits with appropriate teaching in alternative methods.

Consideration 8: Many links exist between the credibility of the field, its teaching, and the build-up of the required academic structures at high-level teaching institutions

The link between quality instruction in alternative approaches in toxicology and the establishment of an academic structure (like dedicated chairs at universities) is not just a coincidence. The two processes are rather intricately linked, and this has far-reaching implications (Leist, 2006). There are many examples illustrating that the mode of instruction can have profound effects on the scientific impact of a discipline. The study of administration, of various technical or artistic subjects, or of classical apprenticeships like nursing, journalism, or restoration has been added to various university curricula, thereby changing not only the public perception of these fields but also their own scientific basis and core – and, not least, their self-esteem. The rise of an established discipline at respected universities always increases the reputation of the discipline, and therefore, also, its public credibility. A further benefit of the academic status is its strong association with independent thinking and a free competition of ideas and arguments purely on the basis of scientific merit. This also eventually contributes to the credibility of the discipline and the perception of its independence from lobbying groups and individual interests. Thus, even though teaching of 3Rs approaches may be achieved in various ways (Dewhurst, 2006; Vedani et al., 2007; Jukes, 2008; Gadgil, 2007; Akbarsha, 2007; Knight 2007a), the above arguments strongly suggest combining the establishment of a curriculum with the buildup of a dedicated academic structure (such as CAAT or the Doerenkamp-Zbinden chairs). In this context, it should be mentioned that the Doerenkamp-Zbinden Foundation has established an extra chair for education in life sciences in Tiruchirappalli, India (Akbarsha et al., 2009). This chair aims to reform the curricula, especially in zoology, but also in other disciplines.

Here, a thought may be allowed on the corollaries of the foundation of dedicated chairs, beyond their roles in teaching and science (e.g. Hartung, 2008c,d; Leist et al., 2008a,b) and with great reverberations on both. Three consequences are particularly worth mentioning.

1. Conceptualization: This is often neglected in the discussion on the research and development (R&D) of new methods (Fig. 2). There is considerable focus on the phase of implementation that follows the R&D and validation stages. It is frequently forgotten, however, that most research in the field addresses technical problems within already established concepts (e.g. Montag et al., 2007; Whitlow et al., 2007; Rothen-Rutishauser et al., 2008; Heindl et al., 2008; Wanner and Schreiner, 2008; Li, 2008a,b;

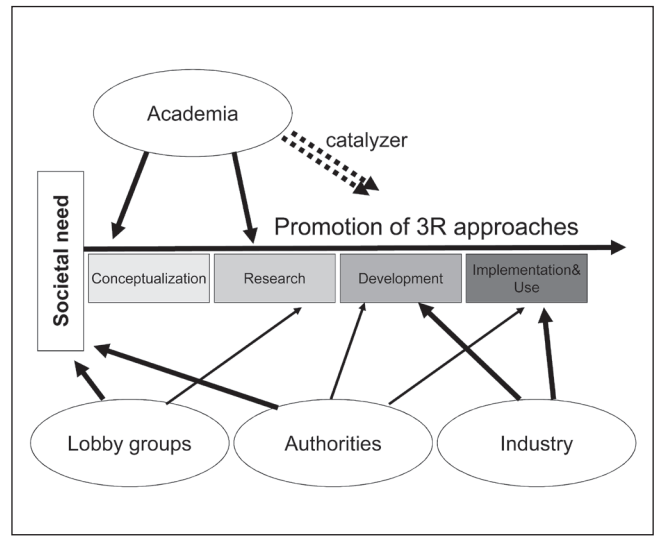

Fig. 2: The role of academia in the pipeline towards alternative approaches in toxicology

Murthy, 2007; de Brugerolle, 2007; González Hernández and Fischer, 2007; Seiler et al., 2006; Henn et al., 2009). For real advances in new areas (e.g. testing of chronic toxicity), entirely new concepts need to be developed. Examples include a report by the Dutch Health Council, *Toxicity Testing, a more flexible approach*, 2001 (Health Council of The Netherlands, 2001) and some other publications (DeJong, 1999; Gubbels-van Hal, 2005; Blaauboer and Andersen, 2007) should be mentioned as well. The most recent milestone was the Toxicology for the 21st Century (Tox21c) initiative (NCR, 2007; Collins et al., 2008; Leist et al., 2008c; Hartung and Leist, 2008). This is based on the overhaul of the way safety evaluations are performed. One notable corollary for future alternative approaches would be to abandon the strategy that has been used successfully for some of the more accessible endpoints required for cosmetics and chemical testing (OECD test guidelines e.g., those on skin irritation and phototoxicity). This old (or "first generation alternatives") approach was often based on not-fully-characterized mechanistic "black-box" models attempting to substitute animal tests on a 1:1 basis. The new approach ("alternatives V2.0") would be conceptually entirely different. This large intellectual step is an example of conceptualization that falls outside the area of standard R&D, and the success of this Tox 21c initiative in involving so many scientists in academia and the regulatory community is certainly linked to its roots in a document produced by a highly reputed academic organization – the National Academy of Sciences of the USA (NRC, 2007).

2. Breaking barriers: At the other (i.e., far) end of the pipeline of method development for alternative safety evaluations (i.e., close to the market) considerable barriers still exist (Fig. 3), despite the documented success of 3Rs methods and problems posed by animal experiments (Knight, 2007b; Leist et al., 2008b; Hartung, 2008a). For instance, technical/scientific barri-

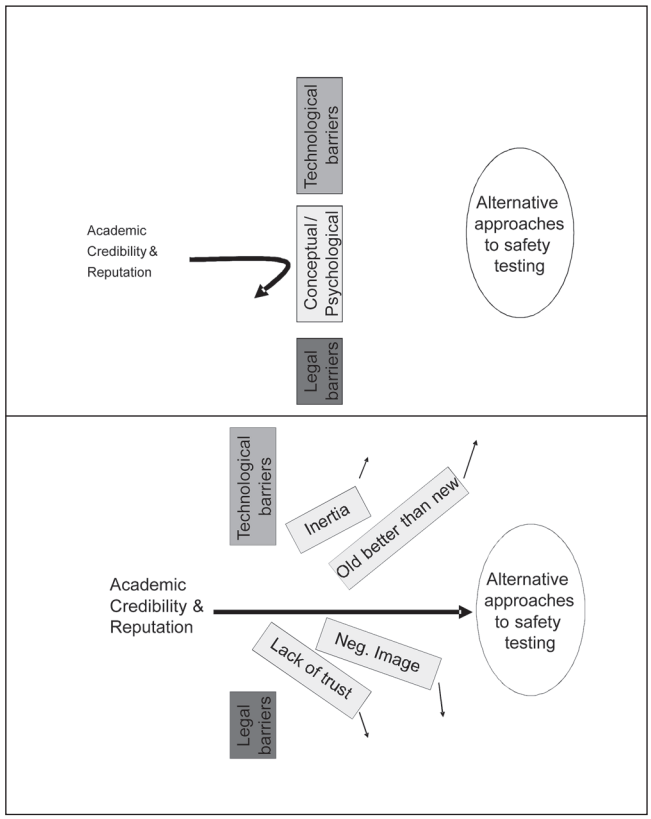

Fig. 3: Breaking conceptual barriers by increased academic reputation

ers are linked to the validation problem (Hartung, 2007b; Leist et al., 2008b). Legal and regulatory issues exist, in addition to conceptual and psychological barriers. The latter are closely linked to the reputation of the scientific area of new toxicology (3Rs methods) outside academia. In particular, end-users and regulators need confidence in the validity of the methods. The transition of new methods is often additionally hampered by inertia and a preference to use old, well-acquainted technology. A lack of trust is also in part of the problem, due to a lack of information or erroneous information about newer methods (Schiffelers et al., 2007). Here, academic institutions and teaching play an important, two-fold role. They contribute to the dissemination of knowledge outside academia through centers like CAAT. Through their independence from lobby groups and their high scientific reputation such groups provide credibility to the validity of alternative approaches, and, by doing so, break down many conceptual barriers.

3. Knowledge transfer: This point concerns the integration of our field of interest within academia. Good scientific work and the resultant academic recognition automatically lead to the integration of the discipline in larger research consortia and with common research efforts at border areas. Besides the integrative function, this is of enormous direct scientific benefit. New technologies and ideas can be imported and developed with specialists of other disciplines (e.g. Mitterhauser and Toegel, 2008; Mertens and Rulicke, 2007). A continuous challenge by, and exchange with, broader scientific areas leads to a maturation and evolution of new approaches to safety testing that would never have been developed from inside the primary field. In summary, the effective integration of the 3Rs field in areas of biomedicine, modern technology, and information sciences has two major benefits. On the one hand, it requires a high academic standard in the field of "new" toxicology for peer recognition and interactions with other disciplines on a level playing field. On the other hand, these interactions guarantee development and dynamics of alternative approaches in toxicology.

Conclusions

The creation by the Doerenkamp-Zbinden Foundation of a series of chairs for alternative methods marks a milestone toward the systematic integration of the 3Rs field into universities and, in consequence, into their curricula. These can serve as a "lighthouse" for other institutions. These pilot projects aim to strengthen their impact by collaboration among themselves and by outreach to other instructional programs.

We are far from having a consistent concept for education of alternative approaches. The suggested means to create this include:

- sharing of teaching materials in a depository
- establishing a network of academic teachers
- a project to develop curricula and channel them to the respective institutions in the various disciplines
- providing support to school teachers

Education represents a key opportunity to advance the field of alternatives. It is largely underexploited so far. Its impact is difficult to measure, but already the attraction and formation of a new generation of opinion leaders will have a major impact, as the first generation approaches the age of retirement. At the same time, the next generation of our "customers" in industry and regulatory agencies will become more receptive to novel approaches. To close with Herbert Spencer: "The principal goal of education is not knowledge, but action." It is time to act.

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