Theme II:
Policy/Law on Animal Use, Public Engagement and Ethics Review

Session summaries for Theme II

Session II-1

Public Accountability

Co-Chairs: Maggy Jennings, RSPCA, UK
Suzanne Fitzpatrick, FDA, USA

Public opinion is influenced by the information that is made available to the public. This session explored the public's perceptions and feelings regarding the use of animals in research. The presentations were made by Dr **A. Krishnaswamy**, Dr **B. T. Reed**, Dr **E. H. Ormandy**, Dr **A. Currie**, and Dr **F. A. Fakoya**. Several common themes ran through all the presentations. They centered on how much and what kind of information is enough, who is the "public", how transparent should organizations be, how do you avoid bias in presenting information, and who should justify the need for animal research.

This session explored the question of who the "public" actually is. It looked at the kinds of information that is currently made available and if this meets the expectations of the public. Does more information lead to a better understanding of the issues surrounding public perception of use of animals in research? When you have such an emotionally charged issue such as research using animals, especially primates, does more information help or hinder public knowledge and acceptance of this research? Or are there some issues were the public has made up its mind regardless of the information that is shared with them?

A discussion of strategies and tools for effective public participation emphasized the importance of identifying your audience – including geographical location, level of education, career choices and demographics. Openness in public information is important – and something that is demanded by the animal protection sector. Expert reviews discussed in the presentation concluded that it is desirable for the public to have information about animal research. However, whose responsibility is it to release this information?

A general theme running through all the talks was the subject of bias. Information must be accurate. But what is accurate – does it mean just correct or does it mean all inclusive? Biases can occur depending on what government or organization releases to consumers. The session debated as to how these biases could be avoided or if they were unavoidable.

The information given need not be voluminous but it should be informative and all bias must be transparent. The discussion centered on information being honest – this means different things to different sectors of the public. Does honest mean showing graphic depictions of animal research or does it mean clearly describing the benefits of the research to the public?

Considerable debate occurred over young people's perceptions of the use of animals in research in the UK. The ethics of animal research became part of the curriculum in some UK high schools. Students at first said they supported research on prisoners and the handicapped over research in animals. However, after the lecture, acceptance of animal research increased significantly. Some in the audience objected to this learning module, suggesting that since the instructor was an animal researcher, the lectures were probably biased. Other argued that "fairness" demanded that opposing points of view should have been presented to the students. The speaker stressed that students must make "informed" decisions but were only presented with one point of view. Part of the curriculum showed very elaborate primate cages, which the audience argued was deceptive in that it was not the norm for this type of research. Therefore the presentation could be called deceptive.

One big debate is the justification for animal research. Since animal research is funded in part by government money, does this give the public the right to criticize or demand that it be stopped? Developing countries are lagging behind in promoting the Three Rs. Possible solutions were discussed. One problematic issue, as demonstrated by public outrage to genetically engineered salmon, is the development of transgenic animals. Interestingly the public is more accepting of this for biomedical research than for food. However, if the public was shown pictures of rodents with human ears growing out of their back, would they be as supportive? Is this being transparent or is it being biased? How you present information to the public has a major impact on the development of attitudes towards research.

The session was very successful in promoting a very lively and spirited discussion about this important topic of public accountability.

Session II-2

Ethics Review

Co-Chairs: Gilles Demers, Canadian Council on Animal Care, Canada
Virginia Williams, National Animal Ethics Advisory Committee, New Zealand

This session focused on the ethical review process, now accepted as a universal requirement for the use of animals in research, testing and teaching. The aim of the session was to discuss the facilitation of this process worldwide so that guiding principles and education/training programs can be harmonized within the context of different legislations, culture, religion and traditions.

The invited speaker was Dr **Maggy Jennings** from the UK RSPCA. In welcoming the widespread development of the ethical review process across the world, Dr Jennings noted the challenges that arise from different approaches to the concept of ethics and the difficulties in translating such concepts into practical review systems. She then went on to explore, through comparison of different national systems, the possibility of development of international guidelines.

Professor **Margaret Rose**, from Australia's University of New South Wales, looked at the historical context of the ethical review process. Raising the possibility that, after nearly 40 years of operation in some cases, such processes may have become politicized, Professor Rose suggested the time has come to review the operation of the process to ensure its effectiveness and engagement with the wider community.

Dr **Andrew Knight** from the Oxford Centre for Animal Ethics took a critical look at the ethical review process from the point of view of the cost benefit analysis, claiming that expected benefits are often based on unrealistic assumptions and that human benefits are rarely sufficient to justify costs to the animals.

Finally, Dr **Virginia Williams**, Chair of New Zealand's National Animal Ethics Advisory Committee (NAEAC), emphasized the importance of the quality of information available to those reviewing scientific protocols to the good decision-making that provides credibility to the ethical review process. In doing so, she detailed the support given by NAEAC to animal ethics committees in New Zealand.

The conclusion drawn from the session was that while systems for the review of research protocols are increasingly well established internationally, their effectiveness remains dependent on the quality of the information available to AEC members, particularly in relation to the proposed benefits of the intended research. With the 3Rs well embedded in the review process, a greater emphasis on ethical justification is recommended.

Session II-3

Public Law – the Three Rs in Regulation Addressing Animal Use

Co-Chairs: Lyne Létourneau, Université Laval, Canada
Paul Locke, Johns Hopkins Bloomberg School of Public Health, USA

The use of animals in research and toxicity testing has led to improvements in public health and welfare and protection against harmful products and chemical exposures. It also has created considerable controversy concerning the appropriate societal controls, in terms of public laws, that should be applicable to animals and research facilities involved in biomedical science.

Following this introduction, this paper seeks to capture the key points from four presentations given at the Eighth World Congress in Montreal, Canada, on August 22, 2011 during the session II-3, entitled "Public law – the Three Rs in regulation addressing animal use." In addition, this paper offers a conclusion that attempts to synthesize the important lessons learned during the session.

As used in this paper, the term "public law" refers to statutes enacted by legislatures and the regulations and policies that support the implementation of those statutes. By selectively examining several legislative efforts, it is possible to begin to understand whether these public laws are effective and what has been achieved through these legislative efforts. An examination of these issues can assist in improving our understanding of the systems of laws and regulations surrounding animal research and allow us to offer suggestions for future improvements and advances in this area.

Jonathan Richmond: *Good regulatory practice: EU Directive 2010/63/EEC, a missed opportunity?*
In 2010, the EU Parliament passed Directive 2010/63/EEC. This directive replaced previous legislation on animals in research.

Because the 3Rs already underlie the previous EU Directive on research animals, this directive cannot be qualified as particularly innovative from the point of view of its overall approach. Nevertheless, there are some elements of novelty within the new Directive (e.g. project evaluation, classification of severity of procedures). However, the Directive is plagued with uncertainties regarding its implementation by member states, especially in areas such as the use of non-human primates and facility inspection.

In addition, there are inconsistencies in the Directive that might blunt its effectiveness. For example, there is a discrepancy between the recitals included in the Preamble of the new Directive and their translation into formal requirements. A very significant example is the discrepancy between the assertion that animals have intrinsic value and all the contents of the new Directive that do not reflect any such intrinsic value. From a philosophical point of view, indeed, a sentient being with intrinsic value should not be used as a means to human ends. However, this is exactly what the new Directive allows.

The new Directive shows that public policy, as enacted in public law, never achieves perfection. Different interests need to be balanced, leading to compromise; concessions are required since it is imperative to reach consensus, especially in a cooperative parliamentary system such as the EU. Nevertheless, the policy objectives underlying the new Directive are most welcomed. Challenges face member states and implementing agencies as the objectives of the new Directive are translated into requirements.

Kathy Hessler and Joyce Tischler: *The US Animal Welfare Act: A regulatory roadblock*
From the perspective of citizens who seek to enforce the provisions of public laws that protect animals in research settings, there are three main problems with the Animal Welfare Act (AWA). First, citizens have no standing to sue. Second, monetary penalties are not assessed against those who violate the law and its regulations. Third, no attorney fees can be awarded. Another weakness of the AWA is that it incorporates only one of the 3Rs: refinement.

While these are important issues, an even more significant failing of the AWA is that it does not protect 95% of the animals used in research (i.e. rats, mice, and birds). The statutory language of the AWA was written so that it appeared that rats, mice, and birds should be covered. However, despite numerous efforts (through litigation and lobbying) by the Animal Legal Defense Fund (ALDF), the United States Department of Agriculture (USDA) was very reluctant to expand the scope of application of the AWA. Today, more than two decades after passage of the AWA, the situation remains the same.

The AWA also can be criticized from a philosophical perspective: it presupposes that all animal experimentation is morally acceptable. Therefore, it does not raise the "utility" question. In other words, it does not ask whether the underlying research is really necessary from a societal and scientific perspective.

The AWA is the major public law in the USA covering animals in research., However, a private law system is created by the US Public Health Service Act has a major impact on animals in research funded by the US National Institutes of Health. Under this private law system, rats, mice, and birds are covered, and other important provisions, such as protocol review by IACUCs, are required.

Derek Fry: *How different countries control animal experiments outside recognized establishments*

Not all biomedical research, testing, and experimentation involving animals takes place in traditional establishments or settings such as academic or governmental laboratory facilities. The assessment of the protection afforded to research animals used outside these traditional establishments and settings requires a two-level analysis. First, it is important to assess how different countries control animal experimentation. Second, it is necessary to evaluate how this control translates to research animals in the wild.

To begin this analysis, caution is required when undertaking to describe the control of animal experimentation. There may be controls that are not apparent to outside observers; and even those entities that are regulated might not have an accurate understanding of their own system.

Certain elements are common to all animal experimentation legislation. These elements include the legal definition of the term "animals," and coverage limited to situations in which the use of animals could inflict pain. The extent of animal experimentation legislation varies between countries according to the meaning and scope given to these two items.

Enacting laws and promulgating regulations are a good start, but they are not sufficient to protect research animals. Implementation and monitoring are key activities. The ability to identify pain in research animals is also crucial, because many provisions aiming to protect research animals are triggered by the recognition of pain in animals. However, many researchers are unable to recognize even evident signs of pain in the animals they work with.

The difficulty of assessing whether an animal is suffering is multiplied in the case of wild animals, where it is even harder to identify pain and distress. Moreover, there are many practical difficulties related to monitoring in such settings. Controls are likely to be either absent or weak. It follows that the application of the 3Rs rests entirely on the researchers, who must be very well trained.

Ngaire Dennison: *From mouse to machine: how have attitudes and individuals affected the progress of the 3Rs in shellfish toxin testing?*

While it is important to understand the strengths and weaknesses of public laws, it is incumbent upon individuals to implement these laws and bring about change. Shortcomings in the regulation of the use of animals in research can be amended by dedicated, well trained. and ethical professionals – the individuals who work in the research community with research animals.

Responsible people can set for themselves stricter standards than those stated in laws and regulations. For such change to happen successfully, however, there must be teamwork and a shared commitment to animal welfare. All the people involved, at all levels (*e.g.* animal care personnel, researchers, project license holder, named veterinarian, certificate holder, inspector) must work together in order to accomplish the desired reform. This means that all those individuals must adopt and share a similar ethical perspective, that they must have or develop the required knowledge and undergo appropriate training so that an ethic of animal welfare becomes a shared value. Perhaps most importantly, for positive change to occur the support of key individuals is required. Leadership must embrace this change and drive the process leading to its implementation.

Conclusions

This session on 3Rs and public law revealed several important themes. First, a system of public laws alone is not a guarantee that animals in research will be treated appropriately. All systems of laws and regulations are by nature imperfect, and their implementation will require an understanding of the underlying purposes and goals of these laws and a commitment to overlook inconsistencies between animal experimentation legislation and statutes in other areas (*e.g.* drug approval requirements). Second, certain public laws, even if enacted with good intentions, can fail to implement the 3Rs due to limitations in the way in which key terms are defined and to procedural shortcomings that do not enable full societal involvement.

Third, to evaluate the 3Rs in non-traditional settings, such as research on wild animals, it is not enough to examine public laws. Attention must be paid to how programs are implemented and monitored, with a special emphasis on the assessment of pain and distress. Ultimately, it could depend upon the skills, training, and attitudes of the researchers. Finally, it is critical to understand that, in certain situations, a robust 3Rs program can exist even if public laws are weak, inapplicable, or non-existent. Individuals, working collectively and sharing an ethical vision of humane science, are more than capable of creating an environment in which the 3Rs will be guiding principles.

Session II-4

Implementing the 3Rs – Alternatives to Legislation

Co-Chairs: Jon Richmond, Independent Consultant, UK
Joanne Zurlo, CAAT, US

This well attended session explored three topics related to non-legislative means of conveying the 3Rs principles: making more effective use of available information on the 3Rs by those writing and evaluating protocols, promoting the 3Rs through voluntary accreditation systems and international guidelines, and assessing scientists' attitudes to the 3Rs in the UK and Canada.

Barbara Grune addressed the problem faced by those planning and evaluating proposals for animal use to efficiently and effectively identify the most relevant and context-specific information relating to the 3Rs. The main challenge is not a lack of information on these topics; rather it is the vast, and steadily increasing, amount of structured and unstructured information already available. In the absence of comprehensive meta-analysis and formal systematic reviews, powerful new tools are being developed for value-added databases, including systematic searches with archiving of findings and more intelligent and intuitive internet search engines. The presentation stressed the potential value of the next generation of internet search engines – semantic search engines – which can use the terms contained in a document to give context to its content. This class of intelligent search engine is already available, in the form of the Go3R database, for use by those needing to know about applying the 3Rs to the biomedical sciences.

Kathryn Bayne considered the role of peer review and recognized voluntary accreditation programs, specifically AAALAC International and its three primary standards for accreditation, in promoting the well-being of animals used for research and testing through education, advice and assessment. This program takes into account the production, care and use of animals, and requires compliance with national and international regulations, policies, and guidelines – with accreditation now also referenced in some funding and contractual agreements. Examples were given of the improvements at times required to secure or maintain accreditation, ranging from improvements in veterinary care, through addressing the 3Rs, and post-approval monitoring. The number of accredited institutions is increasing, with the greatest current rate of growth being in Pacific Rim countries. The discussion also covered OIE's Terrestrial Animal Code which now includes a section on the use of animals in research and education and makes many of the basic 3R principles more readily accessible and practically available to a larger audience.

Nicole Fenwick compared and contrasted the findings of two quantitative surveys using open-ended questions; one conducted in Canada the other in the UK, on scientists' attitudes toward the 3Rs by looking at their knowledge of the 3Rs, and assessing opportunities for, and obstacles to, their promotion. The participants were mainly scientists, but respondents included animal care staff and others. Refinement was the least well understood of the 3Rs, both in terms of its definition and identification or practical examples. Better education could create greater awareness that refinement can produce methodological improvements that would be beneficial to the animals and to the research. Respondents were cautious about the prospect of developing relevant full-replacement technologies. Data sharing and access to unpublished findings were seen as potential means of reducing animal use. The positive attitude of the respondents to reduction contrasts with the missed opportunities for reduction still commonly seen in the scientific literature and more practical measures and strategies to promote reduction at the level of the individual experiment are still required. Another challenge is the need to provide advice on the 3Rs in a timely manner early in project planning process.

Taken together, the presentations confirm that non-regulatory measures can bring benefits to science and its practice, including the improved ability to structure and make sense of information from diverse sources, with a major challenge still being to equip scientists and others with the knowledge necessary to ensure animal welfare concomitant with high quality science locally at the level of the individual experiment.

Session II-5

Validation of 3Rs Alternative Methods

Co-Chairs: William S. Stokes, NICEATM/NIEHS, USA
Joachim Kreysa, ECVAM, Italy

Increasing efforts are being directed at finding improved, innovative methods and strategies that reduce, refine, and replace the use of animals for assessing whether chemicals may cause adverse health effects. Using data from such alternative methods to make regulatory risk assessment decisions will require validation to demonstrate that the proposed decisions made with the alternative methods can provide equivalent or superior protection of consumers and workers compared to existing safety assessment procedures. Consideration and use of appropriate validation strategies early in the test method development process is expected to expedite acceptance of new tools and approaches that will provide improved predictions of safety and hazard and will reduce and replace animal use as well.

Dr **William Stokes** began this session by highlighting the opportunities and challenges for validation of new test methods in the 21st Century Toxicology Testing Toolbox ("*Validation of the 21st Century Toxicology Toolbox: Challenges, Opportunities, and the Way Forward*"). He also emphasized that both early communication with national validation organizations and flexibility in the validation of new tools and testing strategies are essential. The extent of required validation will vary depending on the intended purpose, applicability domain, and existing data for the proposed tools.

Dr **Joachim Kreysa** then discussed post-approval validation issues, using the 3T3 NRU *in vitro* phototoxicity assay as an example ("*Post-approval validation issues: the example of the 3T3 NRU in vitro phototoxicity assay*"). He also emphasized the need for post-approval validation reviews to re-assess test method performance as a potential way to expand alternative test method applicability domain and usefulness.

Dr **Wade Rourke** presented an overview of the development, validation, and regulatory acceptance in Canada in 2010 of an analytical chemical method (HPLC) to replace mice for detection of paralytic shellfish toxin ("*Reduction of animal use through validation of a chemical method of detection for paralytic shellfish toxins*"). He noted that using this assay avoids the use of 40,000 mice per year in Canada, and that it was recently adopted in the US in 2011, where its implementation will have an even greater impact.

Dr Sally Robinson concluded the presentations by challenging the need for *in vivo* acute toxicity tests, questioning the value of such tests in safety assessment ("*The limited value of acute toxicity tests in safety assessment*"). She emphasized the elimination of acute systemic toxicity testing for pharmaceuticals in the EU through a joint stakeholder effort of industry, government, and animal protection groups.

This session provided a snapshot of some the successes that have been realized in validation and regulatory acceptance of 3Rs methods. It also provided insights into the steps necessary to move forward a number of new technologies towards regulatory acceptance, while also recognizing the interim steps that can be taken to ensure their appropriate use to meet specific testing requirements.

Session II-6

Setting Limits and Resolving Conflicts Between the Rs

Co-Chairs: Margaret Rose, University of New South Wales, Australia
Robert Hubrecht, Universities Federation for Animal Welfare, UK

The following is a summary of the main issues identified by the speakers at this session, Dr **I. A. S. Olsson**, Dr **M. Hudson**, Dr **R. Hubrecht**, and Dr **M. Jennings**, and during the following discussion. It was acknowledged that the 3Rs have become accepted as the practical foundation for the implementation of the ethical framework under which research using animals is carried out. However, underlying tensions and differences in values and expected outcomes are on-going challenges which can be masked by the perception of the 3Rs as a "unifying principle". There is a need to acknowledge these underlying differences to find a constructive way forward. Tensions can arise for a number of reasons:-

1. Although Reduction is generally accepted as an obviously desirable aim by all stakeholders there can be tension as to whether the target should be absolute reduction in numbers or whether it should be relative taking into account the scientific output (i.e., reduction in the number of animals relative to knowledge gained or drugs tested). Public perception based on published data of animal usage was identified as being a poor representation of Reduction and an issue that needed to be addressed.
2. Because the 3Rs are three principles, there can be tensions when they suggest conflicting actions. For example, reuse of animals might result in a Reduction in numbers of animals used but may involve more stress for a particular animal, i.e., adversely affecting Refinement. In general, it was felt that numbers should not be reduced where it was at the greater cost to individual animals, although each case would need to be judged on its merits. A concentration on Refinement can distract attention from the goal of Reduction in animal use, by diverting resources or making research more acceptable. On the other hand, given that animals are, and will continue to be, used for the foreseeable future, Refinement is clearly the essential R for these animals.
3. There are real and practical difficulties in defining or using biological criteria to inform species choice on welfare grounds (where the scientific purpose of the study allows such choice). It can be challenging to find data that suggest that some species suffer more or less than others, despite the fact that there are various regulatory requirements to use less sentient species. On the other hand it was accepted that there are public views that favor certain species (e.g., some domesticated animals, monkeys, great apes), and that these have to be taken into account. A better approach is to take into account the behavior, physiology and adaptations of each species and consider how these might impact on any proposed procedures or husbandry.

The importance of researchers' attitudes regarding the need for their research and the ethical and welfare implications of their research were also discussed. These attitudes have implications for identifying what the barriers are to improvements and to eventual replacement of animals in their research. The importance of lay participants in decision making was emphasized.

The discussion focused on how standards of research could be raised. Standards are not equivalent everywhere and instances of poor science or poor welfare occur, even when there is general acceptance that better methods or husbandry have been accepted. It was suggested that changes take time and may require a generational change in some cases. However, it was felt that a more active approach was required and that those carrying out the research would probably wish to be fast-tracked to better methods that improved the quality of science as well as animal welfare. Discussion on ways of encouraging higher standards focused on the barriers to change ("not invented here" mentality, inertia, lack of knowledge/training, etc.), as well as strategies for improvement, such as the broader take up by conferences and journals of published standards and ethics committees.

Session II-9

The EPAA, a Model for Private-Public Partnerships Supporting the Advancement of Three R Approaches

Chair: Cornelis Brekelmans, DG Enterprise and Industry, European Commission, Belgium

The European Partnership on Alternative Approaches to Animal Testing (EPAA) is cooperative venture that spans various sectors of industry and services of the European Commission with the goal of promoting alternative approaches in meeting regulatory requirements. Its unique features include the cooperation between authorities and industry across different sectors and the focus on regulatory compliance. Increasingly, academia and NGOs are involved in EPAA projects. Some EPAA projects involve participation by international organizations and authorities from other regions.

In the additional WC8 session "The EPAA, a model for private-public partnerships supporting the advancement of Three R Approaches," **Cornelis Brekelmans** (European Commission) outlined how the EPAA as a public private partnership fits into the wider policy of the EU on alternative approaches. Animal welfare and the promotion of alternative approaches are firmly anchored in the EU Treaty and EU law. The EU, therefore, implements a series of 3Rs-based policies in the areas of research, legislation, validation and acceptance, and international cooperation. Against this background, the EPAA operates as a voluntary, consensus-based organization of regulators and industrial sectors interested in tangible results, offering the potential for cross fertilization between different sectors that currently are working on the 3Rs in isolation. The strength of the EPAA, however, is not only the implementation of EPAA projects as such, but also the commitment by partners to pursue EPAA-identified priorities in their own sphere of competence.

According to Brekelmans, the basis for the success of the EPAA is a clearly defined policy and legal framework, combined with strong political support, intrinsic incentives for companies and Commission services to share knowledge, an agreement on clear and straightforward principles and procedures, and a willingness to create openness and to share knowledge and expertise with other stakeholders.

Johan Descamps (GSK) illustrated the potential of the EPAA for particular projects by presenting the case of the consistency approach in vaccine lot release testing. This project aims to bring about a paradigm shift away from the classical quality control approach (demonstrate the potency/safety of each batch by testing a few samples using a variable *in vivo* assay) to the confirmation of product consistency by monitoring critical steps (holistic approach) during production. The application of the consistency principle is to demonstrate that each batch complies with the defined quality profile of the clinical lots shown to be safe and efficacious, rather than relying on control of some samples as the sole indicator of safety and efficacy.

Successful completion of the project will result in animal welfare, economic, and scientific benefits. The industrial dimension is significant: 10-15% of all animals used worldwide are used for vaccines, and the majority, an estimated 85%, are used for batch release testing. In addition, EU vaccine production represents 70% of global production, and more than 70% of EU production is exported outside the EU. It is therefore of critical importance to promote the consistency approach at the global level.

In this particular project, the EPAA acts as a platform for industry, academia, and regulators from the EU and other parts of the world, as well as international organizations, to engage in a science-based dialogue that serves to promote the consistency approach at the global level.

Joachim Kreysa (European Commission, ECVAM) highlighted the communication and dissemination challenges facing the EPAA as a public-private partnership. These include: to ensure the exchange of information between authorities and industry across different sectors; to maintain momentum within the EPAA, i.e., to communicate with industrial and political decision makers; and to enhance the communication between those interested in 3Rs for regulatory testing through the EPAA "Market Place Concept." Following this concept, the EPAA tries to ensure a virtual market place, where information-supply meets information-demand, where risk assessors/risk managers meet industry/science, and where scientists/test developers meet industry/regulators. This "market place concept" applies to all EPAA activities, as Kreysa illustrated with several concrete examples. The EPAA will intensify the dialogue with the 3Rs-relevant communities (science and test developers, test users and data producers, data users and decision makers, both industry and authorities). It will continue to create and sponsor opportunities for the 3Rs stakeholder, including NGOs, to meet and to exchange information and, last but not least, to ensure dialogue across the many industrial sectors and to a range of Commission Services involved in different EU-policy areas.

The EPAA Science Award, first given in 2010 and worth up to 100 000 €, serves as a good example of the EPAA Market Place Concept. The goal of the Award is to better engage young scientists and to draw their attention to the enormous potential of modern toxicology, alternative approaches, and regulatory compliance. The objective is to promote the transition from innovative and experimental alternative approaches towards their industrial application and regulatory acceptance. Projects typically will be implemented in cooperation with individual EPAA industry partners or Commission services.

In his presentation, the winner of the Award, **Felix Spöler** of the Institute of Semiconductor Electronics, RWTH Aachen University, outlined his project, "Demonstrating the relevance of the Ex Vivo Eye Irritation Test (EVEIT) as a self-contained *in vitro* substitute for the Draize Eye Irritation Test." For the EPAA, the project was considered an elegant and mechanistically based project with a high proximity to the market that should deliver tangible results in the short term. The approach would contribute to the replacement of the Draize Eye Irritation Test. It addresses a relevant endpoint for all EPAA sectors and brings in biomedical technology that is widely applied. It provides an opportunity for a quantitative evaluation of eye irritation and, in particular, on corneal damage reversibility, allowing a 4 classes classification. The project will be implemented in cooperation with BASF SE. For Felix Spöler, the value of the EPAA award is not just the financial support; probably even more important is the unprecedented access to know-how from regulators and industry, the increased visibility of his scientific work, and the possibility to advance a particular alternative up to regulatory acceptance.

In the second part of the session, moderated by **Odile de Silva**, (l'Oréal), the EPAA invited representatives of other regions to state their interest and position on public-private initiatives and the potential for cooperation at the global level.

Regulators, industry, and animal welfare representatives from the USA, Japan, Korea, and the EU shared their perspectives and experience. In particular, the EPAA was interested in learning about the speakers' views on the value of public-private-partnerships (PPPs) regarding their contribution to science development (do they result in better targeting of research?), to fulfilling regulatory requirements, to covering industry needs, to meeting stakeholders expectations, to providing increased flexibility with respect to timelines (is overall progress quicker with PPPs?), and expanding the potential for cooperation.

Susanne Fitzpatrick (Food and Drug Administration, USA), presented her views on PPPs against the background of how the FDA defines Regulatory Science in order to use new tools, standards, and approaches for the assessment of medical product efficacy, safety, and quality. Advances in regulatory science are critical to effectively translate cutting-edge developments in science and technology into promising products and therapies. The FDA, therefore, is actively involved with scientists from both academia and industry and, together with the NIH, launched a new regulatory science grant program that includes support for novel approaches for transforming toxicology: the development and prevalidation of an *in vitro* battery of alternative ocular irritancy assays to replace acute ocular testing, the integration of organ on a chip" microdevices to produce a Heart-lung Micromachine" for real-time measures of the efficacy, bioavailability, and safety of aerosol-based drugs, nanotherapeutics, and other medical products on integrated lung and heart function. An important feature is the ongoing FDA and NIH staff engagement with the grantees/innovators. The FDA and the European Medicines Agency (EMA) have engaged in a collaborative data sharing and testing effort with academia and industry, spearheaded through the Critical Path Institute (CPI), and have identified and qualified for regulatory submission seven novel biomarkers for detecting drug-induced kidney toxicity in preclinical animal models. Additionally, these markers are being tested for their potential in monitoring kidney toxicity in human studies. A similar pre-competitive collaboration is ongoing for other organ system toxicity markers. The FDA has recently partnered with the Defense Advanced Research projects Agency (DARPA) to work together to facilitate innovation. They held a workshop in June 2011 on new regulatory technologies and tools to develop a human-on-a-chip model for non-clinical testing. DARPA will be announcing funding in this area soon.

Moving from current to newer methods is challenging, and working together to catalyze change is an essential step. There is a clear interest in the EPAA model, considered as new and interesting.

Hajime Kojima (NIHS, JaCVAM, Japan) expressed difficulty in monitoring EPAA activities from Japan and stressed the need for broader visibility. He sees potential for collaboration with the EPAA and exchanges mainly in the area of research and development of test methods. There are ongoing projects in Japan on hazard assessment and test methods essential for the New Chemical Management Policy Ministry of Economy, Trade and Industry): the development of methods based on altered gene expression and of cell assays to detect target organ toxicity and metabolic function. Another initiative is the Agri-Health Translational Research Project (Ministry of Agriculture, Forestry and Fisheries, Japan) on the "Development of novel biomedical devices using animal-derived byproducts (Vitrigel Project)."

Young Na Yum (KoCVAM, Korea) expressed that KocVam, although a young organization, is already very active and interacts with several stakeholders through workshops, training, and by having members of animal welfare protection groups, academia, and industry, etc on their Scientific Advisory Committee. They see the benefit of facilitating communication with industry, academia, regulatory authorities, and the public. They also are active in the context of international cooperation within ICATM, together with ICCVAM, ECVAM, Health Canada, and JaCVAM.

Troy Seidle (HSI) shared his views from the Animal Welfare perspective. The expectations in cooperating with PPPs are, first, the swift adoption of non-animal methods and strategies within and across sectors, as well as the reduction of animal use, as appropriate, in regulatory requirements. The second goal is to help propel "21st century science" in encouraging joint funding initiatives such as in the PPP EU-COLIPA "SEURAT-1", as well as joint lobbying to encourage increased targeted funding (e.g., Human Toxicology Project Consortium). In this context, the European project AXLR8 convened a workshop in May 2011 to address recommendations for priority research under

the forthcoming "Horizon 2020" EU funding program. The vision was developed for a large-scale, interdisciplinary effort based on a public-private-partnership model to further develop the "adverse outcome pathway" paradigm, integrating projects organized around five priority health concerns, together with an infrastructure cluster and overarching coordination action.

Carl Westmoreland (Unilever) gave an overview of a company's experience and expectations as an industry partner in a PPP. Experiences to date have shown that PPPs can facilitate multi-disciplinary research and are an essential part of bringing "new eyes" to the challenges (e.g., EPAA's activities on Computational Chemistry). PPPs also enable greater alignment of academic research to future industry and policy (long-term) needs (e.g., NC3Rs CRACK-IT® scheme). They can serve as good platforms for cross industry sector discussions on the three Rs, acknowledging the different needs of different stakeholders in the area of non-animal approaches. For example, Unilever's driver is not 1:1 replacement of existing animal tests but defining new ways to assure consumer safety.

The way forward for PPPs could be to involve regulators and validation bodies early in discussions on new paradigms for risk assessment. It is clear that the PPP model can increase the overall research funds available in priority research areas. However, can PPPs evolve in the future to look at longer-term research strategies in priority research areas? Can they be used to achieve a more "joined-up" global approach to research strategies in priority research areas, such as how safety may be assured without animal testing?

The presentation by **Tzutzuy Ramirez** of BASF raised similar considerations. Participation in PPPs allows for the development of science and the identification of gaps. Initiatives such as the feasibility study on the extended one-generation study for reproductive toxicity developed by EPAA partners are a tool to achieve regulatory acceptance. At the same time, participation in PPPs contributes to industry needs by promoting alternatives and by enhancing academia involvement and engaging with stakeholders. Overall, PPPs offer a potential and a platform for cooperation while maintaining flexibility in view of timelines.

Public Private Partnerships have their own intrinsic value. They allow for the exchange of new ideas, meeting new people, sharing concepts, and enabling common new understandings in the 3Rs space. They allow for early dialogue between authorities, industry, and stakeholders. They allow alignment of long-term needs for regulation and research. PPPs tend to increase the potential for sharing data and expertise. They are a tool to foster cooperation at the global level.

PPPs are being set up increasingly, and most examples given relate to research projects. EPAA occupies a rather specific position in that it works against a clearly defined political and legal background, focuses on a holistic approach towards regulatory compliance, and operates across sectors. Its actions are taken up by the European Commission both to the European and global level.

Session II-10

Role of International Bodies in Spreading Three Rs Efforts Globally

Co-Chairs: Gilles Demers, Ottawa, Canada
Tsutomu Miki Kurosawa, Osaka, Japan

Background

Recent initiatives to foster application and implementation of the Three Rs have been undertaken by several international organizations. This session covered some of these initiatives and discussed the effectiveness of these efforts in encouraging further implementation of the Three Rs.

Gilles Demers: *The role of ICLAS in the application of the Three Rs*

ICLAS is an international non-profit scientific organization that exists to promote high standards of animal care and use in science. Over the years most ICLAS Programs, including the ICLAS international and regional meetings, have focused on the promotion of the humane use of animals in research through the recognition of ethical principles (including the Three Rs) and scientific responsibilities. Since 2004, the ICLAS Harmonization Program has had a particular influence on the application and implementation of the Three Rs. ICLAS has held meetings every 18 months since 2004 to bring members of the international scientific community together to identify and recommend acceptance of guidelines considered to be suitable as international reference documents. The topics covered include endpoints, euthanasia, ethical review of proposed animal use, training of animal users, and use of genetically modified animals. ICLAS also has developed Guiding principles for animal care and use in these areas. This has led to the publication of a first article in Science (May 2006) entitled "Harmonization of animal care and use guidance," and of a second article on the "International harmonization of guidance on the ethical review of proposals for the use of animals, and on the education and training of animal users in science," (2010). An article on the "Guiding Principles on the Care and Use of Genetically-engineered Animals," in progress, is under revision by the ICLAS Working Group on Harmonization of Guidelines for the use of animals in science. The final document will be published in 2012.

The impact of the ICLAS harmonization initiatives on the application of the three Rs by developing countries, scientists (animal users), scientific journals, laboratory animal science organizations, and international scientific organizations was discussed. More information can be found on the ICLAS website at: www.iclas.org

References

Demers, G., Griffin, G., De Vroey, G., et al. (2006). Harmonization of animal care and use guidance. *Science 312*, 700-701

Demers, G., Brown, M., Gauthier, C., et al. (2010). International harmonization of guidance on the ethical review of proposals for the use of animals, and on the education and training of animal users in science. www.iclas.org

Kathryn Bayne, **J. R. Haywood**, and **Molly Greene**: *The Role of CIOMS in the Application of the Three Rs*

In 1985 CIOMS (the Council for International Organizations of Medical Sciences) published its first *International Guiding Principles for Biomedical Research Involving Animals*. These eleven principles profoundly influenced the development of the *United States Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research and Training*. These principles must be adhered to by institutions required to comply with the recommendations of the *Guide for the Care and Use of Laboratory Animals* (implemented by the Association for Assessment and Accreditation of Laboratory Animal Care International) or the Public Health Service *Policy on Humane Care and Use of Laboratory Animals*. These principles also became a required standard for organizations outside the U.S. that seek funding from the National Institutes of Health. The CIOMS Principles currently are undergoing revision and updating. A committee comprised of individuals representing multiple pivotal animal research and laboratory animal science/medicine organizations has supplemented its input to the writing process through a public consultation period. In this manner an international perspective is achieved. Like the original 1985 principles, the 2011 version is intended to be used by the global scientific community to guide the responsible use of vertebrate animals in scientific and/or educational activities. They are designed to assist ethics committees, animal care and use committees, organizations, societies, and countries in developing programs for the humane care and use of animals, especially those entities operating without national regulations. The updated principles place increased emphasis on the Three Rs, and they also address humane endpoints, alleviation of pain and distress, training of personnel, veterinary care, and several other key elements essential to

promoting good welfare in research animals. It is hoped that the revised principles will be endorsed by other worldwide organizations such as the OIE, as well as key scientific and laboratory animal science/medicine organizations. Perhaps they might also help stimulate a similar update of the U.S. Government Principles.

Reference

CIOMS (1985). International guiding principles for biomedical research involving animals. http://www.cioms.ch/publications/guidelines/1985_texts_of_guidelines.htm

Tsutomu Kurosawa: *Three Rs in the OIE Laboratory Animal Welfare Working Group*

The World Organisation for Animal Health, or Office international des épizooties (OIE), is the intergovernmental organization responsible for improving animal health worldwide. Animal welfare was first identified as a priority in the OIE Strategic Plan 2001-2005. OIE Member Countries and Territories mandated the organization to take the lead internationally on animal welfare and, as the international reference organization for animal health, to elaborate recommendations and guidelines covering animal welfare practices, reaffirming that animal health is a key component of animal welfare. The OIE develops standards through the work of expert ad hoc groups that are convened to develop draft texts for the *OIE Terrestrial Animal Health Code (Terrestrial Code)*. Since May 2005, the World Assembly of OIE Delegates (representing the 178 Member Countries and Territories) has adopted seven animal welfare standards in the *Terrestrial* Code including Chapter 7.8., Use of animals in research and education. Documents on animal transportation, training for laboratory animal veterinarians, and testing on animals also are under revision. These OIE standards will have a worldwide impact on the implementation and application of Three Rs in research using animals.

Reference

Chapter 7.8. Use of animals in research and education of the OIE Terrestrial Code at: http://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_1.7.8.htm

Session II-11

The International Cooperation on Alternative Test Methods (ICATM)

Chair: William Stokes, National Toxicology Program Interagency Center for the Evaluation of Alternative Methods (NICEATM)/National Institute of Environmental Health Sciences (NIEHS), USA

In 2007, the International Cooperation on Cosmetics Regulation (ICCR) tasked the European Centre for the Validation of Alternative Methods (ECVAM), the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), the Japanese Centre for Validation of Alternative Methods (JaCVAM), and Health Canada to develop a framework to promote harmonization of scientific recommendations on alternative toxicity testing methods. The resulting framework was implemented as the International Cooperation on Alternative Test Methods (ICATM) through a Memorandum of Cooperation (MoC) that was signed by CVAM, Health Canada, JaCVAM, and NICEATM-ICCVAM on April 27, 2009. In March 2011, the Korean Center for the Validation of Alternative Methods (KoCVAM) was added as a fifth participant in ICATM. This agreement promotes enhanced international cooperation and coordination on the scientific validation of non- and reduced-animal toxicity testing methods. The tests are more readily accepted by regulatory agencies if there is strong scientific information showing the methods are reproducible and able to accurately identify product-related health hazards.

During this session, representatives from each of the five ICATM participating organizations provided overviews of recent progress and planned activities. Speakers included Dr Joachim Kreysa (ECVAM), Dr **David Blakey** (Health Canada), Dr **Hajime Kojima** (JaCVAM), Dr **Young Na Yum** (KoCVAM), and Dr **William Stokes** (NICEATM-ICCVAM). Presentations focused on the three critical areas identified in the MoC: validation studies, independent scientific peer review, and development of test method recommendations for regulatory consideration. Speakers highlighted a number of advances in the research, development, and regulatory acceptance of alternative methods in areas such as dermal and ocular corrosion and irritation, allergic contact dermatitis, endocrine disruptors, acute oral systemic toxicity, and genetic toxicity. Many of these methods have gained international regulatory acceptance through formal adoption as Health Effects Test Guidelines for the Organisation of Economic Cooperation and Development (OECD).

This session provided an overview of progress that has been made since WC7 and highlighted the fact that early and frequent collaboration among the ICATM participants facilitates more efficient evaluation and international acceptance of alternative methods. Since 2009, ICATM cooperation has contributed to the adoption of seven new international test guidelines for 3Rs alternative methods, including the first in vitro methods for eye and skin safety testing. By communicating and working together, ICATM participants are able to more effectively and efficiently validate, evaluate, and recommend internationally harmonized, scientifically sound test methods that not only can protect human and animal health and the environment but also reduce, refine, and replace the use of animals.