The European Partnership
for Alternative Approaches to Animal Testing

# REDUCTION AND REFINEMENT:
# Combining Excellence in Science and Animal Welfare

## ANNUAL CONFERENCE REPORT

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CHARLEMAGNE BUILDING,
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# EXECUTIVE SUMMARY and the KEY MESSAGES of the Conference

The 6th EPAA Annual Conference welcomed the renewal of the partnership between the European Commission and seven industry sectors to advance 3Rs methods and strategies in the framework of regulatory testing.

The Conference focused on the EPAA's lead theme for 2010 - the clear potential of Reduction and Refinement strategies. The European Commission, the industry partners and the Mirror Group all consider that each of the 3Rs has a specific and significant role to play. So while Replacement remains the ultimate goal, there is a need to develop actions specifically related to Reduction and Refinement, as these 2Rs can, in short timeframes, produce significant savings in the use of animals in testing, and reduce suffering.

They also expressed the conviction that the political, regulatory, economic and scientific incentives for the development and use of alternatives will increase in the coming years. Against this background, they see a definite role for the EPAA as a platform for voluntary cooperation between industry and regulators, with an increasing involvement of academia and NGOs.

In vitro/in silico methods are increasingly being used in integrated testing strategies in the decision-making process, be it for regulatory testing or for discovery research. Gradually, all results of testing and discovery research will be used to enhance the quality of regulatory packages and to make regulatory bodies more confident in taking their decisions on the basis of alternative approaches.

The key messages from the Conference are:

- All three Rs play their own specific role, and therefore deserve full attention, each R in its own right.
- Whilst Replacement remains the ultimate goal, all opportunities must be taken to implement Reduction and Refinement strategies.
- Collaboration and sharing of good practice will continue to be crucial factors in progressing the 2Rs.
- Research potential on the 2Rs is expanding; however, more funding is needed for this potential to be fully exploited.
- EPAA partners should aim for a maximum degree of international convergence on implementing 3R approaches.
- Greater recognition is needed for the contribution that training – of animal scientists, laboratory technicians and people in contact with animals - can make to Refinement approaches.
- Concern for animal welfare, which is a central value in Europe, is strongly reflected in the policies and initiatives of the EPAA and of its individual partners.

## Introduction

The sixth annual EPAA Conference took account of the new EPAA Action Programme, which has been built on the basis of previously-started actions, past achievements and lessons learned. Representatives of the European Commission expressed renewed and strong support for the EPAA as a public-private partnership, in the light of the growing range of incentives for the development and use of alternative approaches. The EPAA and its partners highlighted the importance that all 3Rs have, but made a powerful plea for implementation of Reduction and Refinement strategies so as to achieve immediate substantial progress in reducing the number of animals used and animal suffering.

## A CONVERGENCE OF VIEWS BETWEEN INDUSTRY AND THE COMMISSION ON THE POTENTIAL OF THE 2RS

Whilst Replacement remains the ultimate objective, and the focus of significant work, the use of animals will remain necessary for years to come. It is therefore essential to take full advantage of the opportunities offered by Reduction and Refinement methods.

The mandate of the EPAA relates to regulatory testing, with a focus on specific, well defined endpoints. It is the emphasis on the "known" that allows a search for alternative strategies. However, most animals are used in discovery research, where the "unknown" (i.e. biological processes) are studied, and where consequently animal models remain "absolutely indispensable", as was explained by Richard Fosse, Vice President for Laboratory Animal Sciences Europe at GlaxoSmithKline.

In vitro/in silico methods are increasingly being used in integrated testing strategies in the decision-making process, whether for regulatory testing or for discovery research. Gradually, all results of testing and discovery research conducted throughout product development will be used to enhance the quality of regulatory packages and to give regulatory bodies greater confidence in taking their decisions on the basis of alternative approaches. For **Richard Fosse,** reduction and refinement strategies to increase animal welfare are therefore an essential part of his company's research, development and marketing policies.

Underlining a concern that was echoed by virtually all speakers, Richard Fosse said that particular attention should be paid to refinement. "Within the realities of having to deal with animals, we have an obligation of duty to these animals and we have to ensure that their lives are as optimal as possible". Therefore, "refinement is a key and overarching element since this affects the animals that are there and that are being used. This has an immediate impact".

Industry and Commission share the view on the importance of considering each of the 3Rs on its own merits. For **Antonio Tajani,** Commission Vice President in charge of Industry and Entrepreneurship, "Whilst replacement remains the ultimate objective of our policy, we should not divert our attention from the great potential offered by reduction and refinement strategies, [which] can lead to significant reductions in animals used in regulatory testing, and reduce suffering." For Vice President Tajani, "There are more instances where reduction and refinement initiatives on specific endpoints can have a larger impact than full replacement in areas for which animal testing is limited".[1]

The same message was expressed by **Janez Potocnik,** a founding father of the EPAA and now Commissioner for Environment, and consequently responsible – among other things - for EU Directive 2010/63 on the protection of animals used for scientific purposes, and for the REACH legislation on control of chemicals: "Replacement of animal use has and will always be the ultimate goal of the European Commission. And reduction and refinement are equally important to our strategy to promote alternative methods. Significant animal welfare benefits can be realised quickly this way. In a world where scientific research is crucial and still sometimes uses animals, this is worthy of our support."

## THE ROLE OF THE EPAA AGAINST A BACKGROUND OF A GROWING RANGE OF POLITICAL AND REGULATORY INCENTIVES

The coming years will see an even greater emphasis on alternative approaches and the implementation of 3Rs requirements. Consequently, the potential for action by the EPAA will increase, and partners must be ready to act. This was the key message delivered by Antonio Tajani, Janez Potocnik, John Dalli, Commissioner in charge of Health and Consumer Policy, and Máire Geoghegan-Quinn, Commissioner in charge of Research, Innovation and Science, as reported by Elke Anklam, Director of the JRC Institute for Health and Consumer Protection.

For **Antonio Tajani,** there are strong scientific and economic incentives to explore alternatives - provided alternatives are promoted together with the EU's main trading partners. In his view, every time new legislation is proposed in the EU, particular attention will be paid to the question of how legal provisions in relation to alternative approaches and the 3Rs can be reinforced. Similarly, alternative testing has become a standing issue in the EU's international discussions, whether at the OECD level, or in regulatory dialogue with trading partners.

[1] Position has been made available on the EPAA website

**John Dalli** announced his intention to present in 2011 a new EU strategy for animal welfare, as a follow-up to the 2006 first EU action plan for animal welfare. More emphasis will be placed on monitoring Member States to ensure proper enforcement of EU rules on animal welfare. In Commissioner Dalli's view, new approaches should be developed so as to make progress with EU standards and communicate them to consumers, the sectors concerned and international trading partners. Alongside legislation, other ideas should be explored, including initiatives on communication, education, research, and international actions, as part of a holistic approach.

For John Dalli, the EU legislation on cosmetics sent an important signal to industry and researchers to develop alternatives to animal testing and to promote the overall search for alternative approaches. It raised awareness at the international level of the EU's values on animal welfare, and became the catalyst for international co-operation on the validation of alternatives to animal testing in the framework of the International Cooperation on Cosmetics Regulation.

In the Commissioner's view, "To continuously improve animal welfare must be a political priority for all of us. And often it goes hand in hand with health or economic benefits". As he concluded, "the European Partnership is a remarkable and successful model of how to work effectively across different sectors, and in co-operation between regulators, industry, and other stakeholders."

**Janez Potocnik** made a specific reference to the implementation on the new 2010/63 EU Directive, the application of REACH, and the forthcoming biocides regulation. "The potential for action by the EPAA will increase, and partners must be ready to act," he said. As he put it, "the EPAA is a unique, remarkable and voluntary partnership. Ideas, knowledge and creativity are being brought together, with great success. And there is no better way for industry and the Commission to replace, reduce and refine animal use…and ultimately reduce the suffering of animals".

**Emily McIvor,** speaking as a member of the **EPAA Mirror Group,** saw on a pragmatic basis a huge potential for the EPAA in the years to come. She identified a long list of areas of interest for the EPAA, highlighting the implementation of REACH (in particular the upcoming review and requirements regarding reporting and test methods), legislation on cosmetics, plant protection products and biocides, the new Directive 2010/63, and the new Animal Welfare Action Plan. In her view, attention should also be paid to promoting harmonization of 3Rs best practices in bilateral trade agreements. Emily McIvor urged exploration of the synergies between distinct actions in relation to modern toxicology. For her, the next five years will be important, as they will be marked by developments on all 3Rs, by the increasing delivery of results from ongoing projects, and by growing 3Rs awareness in all sectors.



## REVIEW OF PROGRESS

According to **Gerd Ries,** Vice President Regulatory Affairs for Europe, Middle East and Africa at Johnson & Johnson, and industry co-chair of the EPAA Steering Committee, the EPAA has been an important focus for corporate policy and initiative in relation to the EU political and legal framework on alternative testing. It has made it easier to share expertise and data in a number of cross-company collaborations, thus allowing companies to avoid duplication and make best use of resources.

In his view, 2010 was notable for progress in vaccines, computational chemistry and systems biology, acute toxicity, the thematic review of 3R methods for reproductive toxicity, and identifying the potential of Reduction and Refinement methods. (Detailed information is available in the 2010 Progress Report and on the EPAA website.)

## THE NEW ACTION PROGRAMME 2011 – 2015

Gerd Ries also presented the broad lines of the EPAA new five-year Action Programme, which is based on a critical assessment of the first programme, in 2006-2010, and on likely upcoming scientific, policy and legislative challenges. More selective, and focused, with more clearly-defined priorities in the light of evolving EU sectoral legislation and policies, the new programme aims to address unmet scientific challenges, and to achieve a tangible impact on numbers and welfare of laboratory animals.

More specifically, the EPAA will seek to

- Increase international coordination on scientific and regulatory matters relating to the 3Rs;
- Broaden and establish links with national regulators and legal risk assessors;
- Advance the merits of all 3Rs;
- Identify scientific gaps for developing or optimising alternative methods and help address them through relevant research programmes and research funding;
- Seek the involvement of scientists from diverse areas, to increase knowledge of the 3Rs in the broader scientific community.

The new Action Programme offers scope for a wide range of action, and includes initiatives such as:

- Launching the vaccines project
- Pursuing the thematic reviews
- Consolidating and expanding the sharing of 3Rs good practice
- Making recommendations regarding acute toxicity tests
- Planning dissemination of 2Rs workshop conclusions into "sister" projects.

# KEY MESSAGES FROM THE CONFERENCE

Presentations gave rise to a number of questions and discussion between delegates. The main conclusions can be summarized as follows:

1. **All three Rs play their own specific role, and deserve full attention, each in their own right. Whilst Replacement remains the ultimate goal, all opportunities must be taken to apply Reduction and Refinement methods and strategies.**

   Each of the three Rs has its own role and will bring its specific contribution to the overall aim of minimizing use of animals and reducing suffering. Work should continue to replace animal testing, whilst simultaneously attention is drawn to the potential that the 2Rs offer to enhance animal welfare and increase accuracy in scientific results.

   The EPAA is working to spread good practice between partners and will seek to ensure that the value of the 2Rs is understood and accepted by all stakeholders.

   Presentations drawn from the EPAA October workshop on 2Rs illustrated the progress that has been made on 2Rs, as well as gaps in research and promising paths that researchers could take. Each of these presentations provided a concrete example of how the 2Rs can improve animal welfare: from the COST B24 initiative, to the ICH structure, to examples of reduction and refinement methods used in mouse bioassay test and safety pharmacology, and to the Lhasa database of methods program.

   Extensive research, new findings and novel questions are underway in the area of 2Rs. The EPAA October workshop on 2Rs successfully reflected this activity and generated recommendations to promote further development and application of the 2Rs.

2. **Collaboration and sharing of good practice will continue to play a key role in progressing the 2Rs**

   As Gerd Ries pointed out, "The sharing of data and ideas across sectors is what makes the EPAA 'market place' unique." The conference agreed that this sharing needs to be reinforced in the next five-year action programme, to open up the path to enhanced collaboration, fostering new ideas, and prompting concrete actions.

   Two very potent examples of the contribution that collaboration and data sharing make were presented at the Conference. One is the Animal Model Framework, in which pharmaceutical companies share information about the validity of safety pharmacology models, and which also provides a cross-company database of excipients hosted by Lhasa Ltd - a research centre hosting a number of chemical databases making it possible to share information on toxicity testing.

   The other example is the Long-range Research Initiative toolbox created by the European Chemical Industries Federation (CEFIC), which helps companies access the results of chemical industry research programmes.

   A presentation on training of refinement and reduction methods outlined the different pan-European training programmes that the Federation of European Laboratory Animal Science Associations (FELASA) is putting in place for laboratory personnel and other employees whose work involves handling of animals. The EPAA will seek to strengthen collaboration with FELASA.

3. **Research potential on the 2Rs is expanding, but needs more funding to be fully exploited**

   The need was noted for further research into the choice and development of 2Rs methods, to ensure that they are scientifically valid, are truly beneficial to animals, and do not detract from the scientific integrity of the research.

   Funding for research into 2Rs methods must be increased. Suggestions at the Conference pointed to the 7th Framework Programme as an opportunity to attract support in areas where laboratory animals are used for research on refinement and reduction. FP7 should include all the 3Rs in all areas where laboratory animals are used.

4. **There must be channels to ensure research findings can be translated into practice**

   Identifying gaps and spending money on research will have minimal impact if the research is not translated into practice, as several examples presented at the Conference underlined.

   Through its LRI program, CEFIC makes €150 million of research findings and tools accessible and available online. It is important to bring key people in the field together to consider how to increase dissemination and adoption. This would include ranking research; informing users about the capabilities of various tools; creating portals that will guide users to relevant research; and ensuring that the data is formatted so that it is presented and can be downloaded in a way that is compatible with regulatory requirements.

   Based on research on the impact of analgesia on outputs in mice used in product development, the suggestion was made to develop standardised pain treatment protocols from the observed behaviours of mice, taking account of research to determine the impact of pain killers on animal wellbeing and on data generated in tests.

   Based on a presentation regarding the Mouse Bioassay in Shellfish Toxin Testing in the UK, a strong plea was made for improving the institutional setting to promote alternatives, and to reduce dependence on poor quality "gold standards", over-specification of methodology, and "engineering" rather than "performance" standards.

5. **EPAA partners should work towards establishing maximum international convergence on implementing 3Rs approaches.**

   It is important not only to ensure that 2Rs research is translated into practice, but also to achieve this without disadvantaging companies in the EU with regulations that exceed requirements elsewhere. Further international cooperation and coordination are needed to ensure satisfactory and equivalent conditions.

   The ICH is an example of sharing good practice. It promotes the harmonisation of ways to meet regulatory requirements in the pharmaceutical industry, so as to eliminate the need to duplicate animal studies for US, EU and Japanese regulators. It is critical to maintain efforts to ensure that Japan, the US and the EU work together on implementing 2Rs.

   In the same way, test methods needed for REACH should preferably be adopted and implemented under the OECD auspices.

   Similar arrangements on translating 3R results into practice should be developed in other sectors.

6. **The training of animal scientists and handlers must be recognised as a key contributor to refinement methods**

The way in which animals are handled has obvious implications for their welfare. But it also affects the results of tests: if animals are trained in the procedure and are familiar with the staff, their response will be better.

Animal scientists also need to be trained to make behavioural assessments that provide indicators of impaired well-being.

Education and training of animal care personnel underpins the 3Rs. The quality of this training is critical and it is essential to implement accredited training and attainment standards across Europe.

7. **The concern for animal welfare, a key value in European policies, is strongly reflected in the policies and initiatives of the EPAA and of its individual partners**

EPAA and its partners are committed to animal welfare, which underlies the search for 3Rs approaches. Reducing the number of animals used in individual tests makes an obvious contribution to better animal welfare. So do refinement strategies, such as using analgesia, administering test substances orally rather than by injection, or limiting the duration of a test. In addition, providing the most appropriate housing will ensure better living conditions for animals in laboratories and generate the best possible science.



## POSTER AWARDS AND THE LAUNCH OF THE EPAA AWARDS ON SCIENCE AND COMMUNICATION

One way in which the EPAA is improving communication and awareness across sectors is through its awards - for the best poster, the best communication about the 2Rs, and the best science to advance the application of the 3Rs.

The winners for the best poster were **Derek Fry** and **Michelle Hudson** of **FRAME** - the Fund for the Replacement of Animals in Medical Experiments - for the poster "Training for Reduction". A recognition for the best poster from industry was given to **Volker Strauss** and colleagues at **BASF** for the poster "Reduction through refinement: the application of metabolomics in vivo under REACH", describing how metabolomics can be applied in pre-screening to reduce in vivo testing of chemicals under REACH.

The **EPAA Communication prize** went to **Sarah Wolfensohn** for her article, "Alternative Approaches to Animal Testing - the challenges and limitations" in which she gives a clear explanation of a technical topic, namely this year's theme: the opportunities and limitations of 2Rs (Reduction and Refinement) approaches within the context of product development and safety.

The **EPAA Science Award** was given to **Felix Spöler** of the **Institute of Semiconductor Electronics of the Rheinisch-Westfaelische Technische Hochschule** for his project, "Proving the relevance of the Ex Vivo Eye Irritation Test (EVEIT) as a self-contained in vitro substitute for the Draize Eye Irritation Test".

The EPAA considers Dr Spöler's project a sophisticated and mechanistically based project with a high proximity to the market that should deliver tangible results in the short term. The approach has the potential to provide a stand-alone replacement to the Draize Eye Irritation Test. It addresses an emotive and relevant endpoint for all EPAA sectors. It exploits widely-applied biomedical technology, and provides an opportunity for a quantitative evaluation of eye irritation.

## CONFERENCE REGISTRATIONS

Close to 200 persons registered for the Conference, from the European Parliament, national and international authorities, Commission services, EU agencies, industry, academia, animal welfare organisations and consultancy.

Programme and presentations are available on the EPAA website, http://ec.europa.eu/enterprise/epaa/index_en.htm

The EPAA Progress Report of 2010 and more information about EPAA is available at

**www.epaa.eu.com**

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