The European Partnership
for Alternative Approaches to Animal Testing

ANNUAL REPORT 2009

EPAA | The European Partnership for Alternative Approaches to Animal Testing
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Foreword

It is our pleasure to present to you the EPAA 2009 Progress Report, adopting a new and more user-friendly format.

We believe that the EPAA has made steady and serious progress on how alternative tests can be developed and brought into widespread use for meeting regulatory requirements. Work within EPAA has brought new insights and achievements during 2009. This report provides highlights of the accomplishments of the year, and an outline of how the actions taken by EPAA are contributing to progress in the 3Rs in Europe and beyond.

During 2009, we chose to pay particular attention to dissemination of the 3Rs. Discussions we had with other organisations active in the field of the 3Rs proved that this was a challenging choice. Dissemination is an ongoing task, and we will seek your views on the way forward during the 2009 EPAA Conference.

In 2009 we also examined how we can better organise our work in order to improve our efficiency. In view of the increasing number of projects currently underway, and the resources available, we decided to create three main platforms to replace the original five Working Groups.

We take this occasion to thank all those who have been working for the EPAA: industry, Commission services, academia, NGOs, and - last but not least - the Mirror Group.

The EPAA was created for an initial period of five years. EPAA partners consider that it is capable of promoting the 3Rs in regulatory testing effectively, and have therefore expressed their wish to continue their unique and challenging cooperation.

Georgette Lalis
European Commission
Commission Co-chair Steering Committee

Odile de Silva
L'Oréal,
Industry Co-chair Steering Committee

What is EPAA?

The European Partnership for Alternative Approaches to Animal Testing (EPAA) is an unprecedented collaboration between the European Commission and major companies from seven industry sectors. It is a partnership in which knowledge, research and resources are pooled to accelerate the development, validation and acceptance of alternative approaches for regulatory use, and in which best practice is shared to promote the use of 3Rs methods.

Overview of EPAA activities in 2009

The year has seen concrete developments in optimising existing validation and acceptance mechanisms and provoking new thinking about alternative approaches.

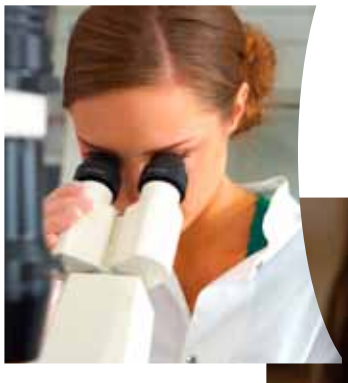
Promoting cutting-edge research will pave the way to the accelerated development of alternative approaches to assure safety. EPAA has identified areas that merit further attention to create new approaches – such as computational chemistry and stem cell technologies. This scientific expertise feeds into the focus of the EU's research programmes.

Engagement with regulatory authorities has promoted reviews of testing requirements and a joint search for adaptations that can reduce the need for using animals.

EPAA's cross-sectoral membership has two particular benefits: it enables broad collaboration and sharing among the partners of practice and experiences across sectors, and at the same time it makes it possible to disseminate information and promote 3Rs-oriented activities to the wider world. In addition, EPAA has identified the potential for promoting the 3Rs and achieving major savings in the use of animals at the level of individual sectors, such as for chemicals and for vaccines, where decisions have been taken to follow-up activities in 2010.

PROSPECTS FOR FASTER VALIDATION

One contribution to making the validation of alternative approaches easier is to put the relevant data and information in the right place at the right time. EPAA created a standardised format and agreed a number of principles, so that validators' calls for information and substances are more effective, and responding to the calls is easier and more efficient.



An improved framework for sharing information and substances was created in light of actual calls for data and substances for test validation, as well as systematic data sharing between individual companies and the European Commission's European Centre for Validation of Alternative Methods (ECVAM). This new framework is open also to non-EPAA companies interested in promoting the 3Rs.

Four EPAA companies received a request by ECVAM and they all agreed on a framework to provide data and substances to support an eye irritation validation study which uses in vitro human reconstructed models instead of in vivo models using animals. EPAA has also had significant input into ECVAM's planning for a repository of chemicals which is designed to speed up validation projects. Dialogue between ECVAM and EPAA clarified points of ambiguity and addressed concerns amongst EPAA companies on issues such as confidentiality, rights, and access. Revision of new method submission forms facilitated the start of a pre-validation study for three in vitro methods in the area of skin allergy developed under the Colipa research programme. Colipa and ECVAM collaborate closely in this activity.

RESEARCH PLANNING IS MORE EFFECTIVE

EPAA has created databases which allow cross-sector reapplication of the best available science. In parallel, in partnership with scientists from different disciplines, EPAA is exploring new avenues for 3Rs research.

Planning is underway for a workshop in the first half of 2010 on exploiting computational chemistry and systems biology in safety testing, through novel approaches that can assess liver toxicity without the use of animals. Discussion will focus on intrinsic chemical reactivity (towards proteins or DNA), biologically-specific chemical interactions (such as receptor-based interactions or enzyme inhibition), integration of chemical interactions with initial biological consequences (metabolism, response to interference with macromolecules, disturbed cellular metabolism), integrative bioinformatics and systems effects, and quantitative aspects (dose responses, kinetics etc).

Stem cells in safety testing was examined at a workshop at Ispra in October, to assess the role that stem cells could ultimately play in novel approaches for the characterization of the potential hazards of chemicals and drugs. EPAA is providing guidance on priorities for current research on the use of stem cells in testing strategies for safety assessment under REACH and the 7th Amendment of the Cosmetic Directive. It is also helping to ensure that in future calls under EU research programmes, findings of existing projects are taken into account in order to avoid duplication of work and allow faster progress.

In its November 2008 workshop on "in vitro ADME in safety testing"(the report will be published by end 2009), EPAA examined how Absorption, Distribution, Metabolism, and Excretion in vitro test systems could be blended into Integrated Testing Strategies (ITS). Because one of the integrated systems of interest was physiologically based pharmaco/toxicokinetic modeling (PBP/TK), and how in vitro generated data could help predictive toxicology, a PBP/TK exchange forum is being established to explore how the models widely used in pharma and agrochemical could be deployed in other sectors. Bringing together the experts among developers and users to compare and improve the use of the different techniques will raise awareness across different sectors and provide a forum to present developments and exchange views, bringing additional coherence and mutual benefit to projects under EU research programmes.

POTENTIAL FOR REDUCTIONS IN ANIMAL USE IN ACUTE TOXICITY TESTING IDENTIFIED

Acute toxicity testing still requires the use of animals in several sectors, and therefore EPAA has focused on this as a key area in which to identify opportunities for maximising the use of 3Rs. Because EPAA brings together a wide range of industry sectors, it has a unique overview of the regulatory and scientific issues in this field, and can recommend approaches that could be adopted widely across different sectors.

Retrospective data analysis conducted by ECVAM, Humane Society International and the UK National Centre for the Replacement, Refinement and Reduction of Animals in Research looked at the possibility of omitting one of the three routes of administration in acute toxicology studies mandated for classification and labelling purposes. EPAA will help to promote the findings of the studies and sponsor a workshop in February 2010 to discuss with regulatory authorities specific proposals for waivers that would deliver direct 3Rs benefits.

An EPAA survey on the drivers and methodology of acute toxicity tests in different sectors obtained a response from 18 companies, and this information has fed into an EPAA paper on the subject which will be submitted for publication in 2009. The survey revealed that the key driver is classification and labelling. It also showed that certain stated reasons for testing are not supported by the information generated from the studies. And most importantly, most companies confirmed that they would be ready to skip the dermal testing route if a robust set of data supported the possibility. It also became evident that in-depth regulatory dialogue, within and across sectors, is necessary to make best use of the many 3Rs efforts in this field, and to take account of the complexity of the regulatory landscape.

Acute toxicity testing is a requirement in most sectors. The requirement has been successfully challenged within the pharmaceutical sector (Regulat. Toxicol. Pharmacol. 2008; 50, 345-352; ICH M3 R2, Recommended for adoption, 11 June 2009) where it could be established that necessary data are available from other studies. Now, the requirements for acute toxicity testing and 3Rs possibilities are being investigated in other sectors.

BRINGING NEW EFFICIENCIES TO SPREADING INFORMATION

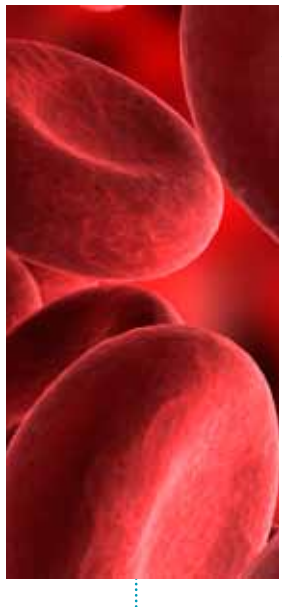
EPAA took as its theme for 2009 the dissemination of 3Rs information. As a first step, it conducted a fundamental review of how to improve targeting and delivery, to speed progress towards adoption of 3Rs, raise the profile of 3Rs research and increase acceptance by the regulators.

A survey commissioned by EPAA in May 2009 assessed the views of target audiences about the dissemination of 3Rs information. It allowed sharper profiling of these audiences, highlighted gaps, and generated recommendations about which further audiences should be addressed, and how. The recommendations included boosting access to information, raising the profile of 3Rs research, and improving the quality of dialogue with regulators.

The potential of networking among webmasters and of developing synergies fostered by EPAA was explored with a view to deliver relevant scientific information to different audiences. These synergies would build on existing information and promote quality sources of 3Rs information, so as to benefit uptake and acceptance.

Instead of investing in expensive web portals of questionable effectiveness, EPAA's preference is to sponsor events promoting scientific dialogue among method developers and users and regulatory authorities, in areas such as acute toxicity, reproduction toxicity or vaccine quality testing.

Other ideas are still in development, including the creation of an EPAA award to attract new scientists/sciences to 3Rs and to raise the profile of 3Rs research and encourage communication about 3Rs.



Examples of activities that could benefit from wider dissemination

Reducing animal use in reproduction toxicity

Companies within EPAA have been examining the feasibility of replacing multi-generational reproduction toxicity tests with a single extended one-generation study. All the work is expected to be completed by early 2010, when a workshop will be held to disseminate the results. The aim is to assess the scope for wider application in testing strategies being developed – particularly for regulatory testing under the EU's REACH legislation. The potential animal welfare benefits include refinement and up to a 40% reduction in the number of animals used compared to the two-generation study.

Assuring vaccine quality while reducing animal tests

Preparations advanced for an ECVAM/EPAA workshop in January 2010 to explore how animal testing might be reduced in routine quality control for human and veterinary vaccines, by the use of the so-called consistency approach. Since vaccine quality is the consequence of strict application of a quality system and of consistent production of batches, agreed product characteristics can be tested in vitro during the manufacturing process of a batch and shown to be similar to those of batches demonstrated to be safe and effective in clinical trials. This principle has already been used for some novel human vaccines, and wider deployment could cut animal use substantially, since current tests on each batch of a vaccine involve large numbers of animals.

COOPERATION BETWEEN INDUSTRY AND REGULATORS IS BECOMING STRONGER AND MORE TANGIBLE

By the very nature of the partnership, and the exchange of expertise, data and knowledge between industry and authorities, the work between European Commission services and industry partners in the EPAA has helped make further progress in more widespread application of 3Rs in the regulatory framework. Concerns, ideas and suggestions stemming from work in the EPAA feed into the activities of several Commission services. Links with ECVAM have provided a basis for specific proposals such as the revision of the new tests submission requirements to speed up and simplify validation and acceptance of alternative methods.

In the context of a debate with the European Parliament, the European Commission has streamlined regulatory acceptance processes for new alternative approaches, thus meeting also recommendations made in various EPAA workshops. EPAA companies have an important role in supporting the implementation of procedures in the wake of the Commission's dedication to speeding up validation and acceptance processes, by providing appropriate feedback and data necessary to complete procedures.

Following a joint analysis by European Commission services and EPAA industry partners of the test submission system for validation at ECVAM, the forms have been made more user-friendly to secure provision of data that would make it possible to prioritise the most relevant methods according to a set of principles agreed in 2007 by the EPAA partners. ECVAM is working on a web based step-wise test submission procedure, starting with a pre-submission form that serves as the basis for an initial assessment of the potential of a suggested new test method.

The need to promote validation and acceptance at the global level is evident. In light of the regulatory concern highlighted within the EPAA context, and at the instigation of the International Cooperation on Cosmetic Regulation (ICCR), the organisations responsible for the formal validation of alternative methods in the EU (ECVAM), US (ICCVAM), Japan (JaCVAM) and Health Canada set up the International Cooperation on Alternative Test Methods (ICATM). The reorganisation of the ECVAM's peer-review system will also pay particular attention to supporting the harmonisation of international validation standards in order to enhance international acceptance. EPAA contributes to discussions on the restructuring of the peer review process employed by ECVAM's Scientific Advisory Committee (ESAC), which will create conditions conducive to wider publication. The publication of the peer review documents and of the peer-reviewed reports should help prevent repetition in the USA or Japan. In addition, the promotion of 3Rs has become a standing issue on the agenda of regulatory dialogues between the European Commission and the EU's main trading partners, such as the Transatlantic Dialogue.

R&D priorities identified by EPAA partners are taken into consideration in the implementation of FP7. Conversely, EPAA industry partners are expected to encourage follow-up to calls for proposals that address the priorities identified by EPAA.

EPAA's scientific work on Integrated Testing Strategies (ITS) will constitute an important input to regulators with regard to validation and acceptance. To help establish validation principles for ITS, EPAA is aiming to tackle outstanding questions not yet answered - such as the need for validation (and to which degree) of building blocks vs. the whole strategy. A November 2008 workshop was based on case studies from industry and on fundamental research on skin sensitisation, eye irritation, PBPK and mutagenesis, and involved regulators from the European Food Safety Authority (EFSA), the European Chemicals Agency (ECHA), the Scientific Committee on Consumer Safety (SCCS), statisticians, independent institute members, researchers and industry.

A second workshop took place in October 2009 and brought ECVAM and industry participants together with representatives from ECHA, the European Medicines Agency and the Organisation for Economic Co-operation and Development to discuss further to which extent the existing validation principles are applicable to the validation of ITS. It was based on case studies from acute toxicity and skin sensitisation, and took account of experience gathered in the areas of in vitro tests and Quantitative Structure Activity Relationships.

EPAA has launched an initiative to list tests that are currently facing roadblocks for international regulatory acceptance to feed into further dialogue with regulators from international bodies.

EPAA partners

European Commission

- DG Enterprise and Industry
- DG Research
- DG Environment
- DG Joint Research Centre
- DG Health and Consumer Protection

Companies

- Abbott
- Astra Zeneca
- Avon
- BASF
- Bayer
- Beiersdorf
- Boehringer Ingelheim
- Chanel
- Colgate-Palmolive
- Dow
- DSM
- Elizabeth Arden
- Estée Lauder
- Evonik/Degussa
- Glaxo SmithKline
- Henkel, Phenion
- Johnson & Johnson
- Kanebo
- Kimberly-Clark
- L'Oréal
- LVMH
- Merck
- Merck Sharp and Dohme
- Novartis
- Novo Nordisk
- Novozymes
- Pfizer
- Procter & Gamble
- Reckitt Benckiser
- Roche (F. Hoffmann-La Roche)
- Sanofi-Aventis
- Schering-Plough
- Serono
- Shiseido
- Solvay
- Syngenta
- Unilever

Small & Medium size Enterprises (SMEs)

- Euroderm
- StratiCELL

Federations

- Soaps and detergents (AISE)
- Chemicals (CEFIC)
- Cosmetics (COLIPA)
- Crop Protection (ECPA)
- Pharmaceuticals (EFPIA)
- Bio-Industries (EuropaBio)
- Animal Health Europe (IFAH-Europe)

With a view to increasing efficiency, EPAA is reorganising, maximising coordination on the cross-cutting themes that are central to extending the use of 3Rs. It now operates through three platforms – one focused on scientific issues, one on legislation and acceptance of alternative methods, and one on dissemination and communication.

EPAA projects underway...

- Technology transfer: extended one-generation study for reprotox
- New perspectives on safety - follow-up: Computational chemistry and systems biology
- New perspectives on safety - follow-up: Stem cells
- Acute toxicity testing
- Exploring opportunities for monitoring the uptake of 3Rs in practical implementation under REACH
- Workshop on biologicals/vaccines (veterinary and human)
- Address barriers to validation & Support of ongoing validation studies
- Address barriers to regulatory acceptance
- Validation of ITS
- EPAA 3Rs databases
- Enhance dissemination of 3Rs information to target audiences
- EPAA award
- External communication
- Internal communication

Governance

In 2009, the EPAA Steering Committee met on 26 March, 16 June and 18 September. A fourth meeting is scheduled for December 2009.

The Mirror Group met on 22 April and 17 September, expressing support for ongoing and envisaged EPAA work, providing valuable suggestions and advice.

Minutes are made available on the EPAA website.

Work in EPAA working groups and projects attracted an increasing number of participants of non-governmental organisations.

The EPAA continued to implement an active communication policy especially through its revised website, newsletters and contributions in several 3Rs-related scientific conferences. In addition to the special session on EPAA activities in the VII World Congress on Alternatives (WC7, Rome) and numerous references to the EPAA made by EPAA partners, EPAA was invited to give a presentation of its activities and the potential for 3Rs in regulatory testing at the 20th anniversary event of ZEBET on 27 October and in the special session on alternative methods and risk assessment at the 5th Meeting of Chairs and Secretariats of EU Commission and Agency Scientific Committees and Panels involved in risk assessment in Brussels, on 19 November 2009.

Further info is available at **www.epaa.eu.com**

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