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The European partnership for alternative approaches to animal testing

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Abstract
In the light of an increasing tendency to introduce the 3Rs into European law – often in a very specific and prescriptive fashion - European industry representing 7 large sectors and the European Commission, created in November 2005 the European Partnership for Alternative Approaches to Animal Testing. Its aim is to better promote the 3Rs in regulatory testing by adopting a holistic approach to acceptance of alternatives, from validation and regulatory acceptance, harmonization of global acceptance of new approaches to more effective dissemination of good practice in order to ensure widespread use and implementation.

The initial premises on which this unprecedented cooperation between industry and authorities was based have been confirmed, i.e. that significant scope exists to promote the application of the 3Rs, through practical sharing of the experience, knowledge and technical know-how between the Partners, and across the industry sectors and Commission services, and through the application of new, research led, science and technology which offer scope for completely new approaches to deriving the required safety information.
The article also shortly indicates the EPAA longer term ambitions.

Keywords: 3Rs, regulatory testing, European Union, validation, regulatory acceptance

An ever increasing European legal incentive towards 3R approaches.

Animal welfare has been an important policy issue in the European Union since 1986 when the concept of the 3Rs was introduced in European law by Directive 86/609/EEC[1]. The directive obliges EU Member States to enforce this concept in their respective territories.[2]

The Treaty of Amsterdam[3], signed on 2 October 1997, introduced a Protocol on animal welfare. According to this Protocol, the European Community and its Member States shall, in formulating and implementing the Community's agriculture, transport, internal market and research policies, pay full regard to the welfare requirements of animals, while respecting the legislative or administrative provisions and customs of the Member States relating in particular to religious rites, cultural traditions and regional heritage.

The full extent of these provisions became particularly clear in the subsequent discussions regarding modification of the EU Directive on cosmetics products.[4] The 7th Amendment of the Cosmetic Products Directive[5] introduced a ban on animal testing of final cosmetics products. This reflected the prevailing rationale that the safety of final products could be assessed on the basis of an assessment of ingredients. As regards ingredients, the 7th amendment also introduced a phase-out of any animal testing for ingredients with deadlines of 2009 and 2013 dependent upon the complexity of the endpoint. Tests concerning repeated-dose toxicity, reproductive toxicity and toxicokinetics will be subject to a ban at the later deadline of 2013.

Legal provisions concerning the 3Rs were introduced also via the new EU regulation on chemicals, the so-called REACH.[6] REACH is based, inter alia, on the acknowledgement of the need to assess the safety of chemicals on the European market. Given the scale of testing of chemicals mandated, REACH also introduced legally binding mechanisms to replace, reduce and refine animal testing.

Most recently, the European Parliament and the Council are discussing a proposal[7] for revision of the Plant Protection Products Directive.[8] Also in this context, legally binding provisions in relation to the 3Rs are under consideration.

In the light of this increasing tendency to introduce the 3Rs into European law – often in a very specific and prescriptive fashion - European industry representing 7 large sectors and the European Commission, decided to join forces in order to better promote the 3Rs.

The European Partnership for Alternative Approaches, the EPAA, was officially launched at a Conference in Brussels on 7 November 2005, based on a 3Rs Declaration, jointly subscribed to by the European Commission and participating industry. From its inception, it benefited from a strong personal commitment from the EU Commission's Vice President Guenther Verheugen, the Commissioner in charge of Research, Janez Potocnik, and the then Vice President of the European Parliament, Dagmar Roth Behrendt.

The Objectives and Action Program of the EPAA.

The Partnership between industry and the European Commission seeks to promote the development, availability and acceptance of alternative approaches to animal testing in regulatory testing.

Given the focus on regulatory testing, the partnership does not deal with aspects of animal use related to fundamental research or product development. Consequently, about 20 – 25 % of all animal testing is thought to be covered by the EPAA activities.

The focus on regulatory testing permits close cooperation between those who are obliged to conform to regulatory requirements, and those who are in charge of coordinating development and implementation of regulatory demands on testing throughout the European Union. This approach is one of the cornerstones for a dynamic and ambitious program to accelerate the implementation of alternative methods.

The EPAA is not involved in regulation or legislation, but in implementation of legislation.

During the first months of its existence, partners carried out extensive consultations among a wide range of experts drawn from industry and European Commission services. The action plan was determined on the basis of a realistic assessment of needs and potential to make progress, built around five interconnecting themes.

The EPAA Action Programme was adopted in May 2006. It identifies a number of concrete activities to take place over an initial period of 5 years,

- Mapping of past and current 3R activities to better inform the planning and prioritisation of subsequent actions
- Prioritisation, promotion and implementation of future research based on the application of the 3Rs
- Identification, dissemination and implementation of best practice in the use of the 3Rs
- Implementation of the 3Rs in regulation and decision making
- Validation and acceptance based on the 3Rs

In the light of progress made, the Action Program is under revision to make it more focused and enable better integration of future activities. There are clear indications already that the initially adopted themes are still appropriate and their potential impact has been confirmed. The revised Program is therefore not expected to entail radical changes but rather constitutes a mid-course adjustment of the original plan.

Who is involved in the EPAA?

Different parties take part in the EPAA, as partners, participants or as members of the Mirror Group.

Partners in the EPAA are the European Commission, individual companies from 7 industrial sectors and their European trade federations., i.e. those directly involved in establishing regulatory compliance.

The European Commission is represented by all its services which are dealing in some way with animal testing and are bound by the EU Treaty to promote 3R approaches where possible. These are mainly the Directorate General (DG) for **Enterprise and Industry (** cosmetics, pharmaceuticals and chemicals, soaps and detergents, biotechnology), **Consumer Protection and Public Health** (plant protection products, animal welfare, food and feed, an area where new EPAA activities are likely to be started in 2008), **Environment** (chemicals, in particular REACH, protection of animals used for experimental and other scientific purposes, currently under revision), **Research (**European Research Framework Programmes) and the **Joint Research Center (**ECVAM, the European Center for the Validation of Alternative Methods).

By their privileged contacts with their national counterparts and in charge of the coordination of implementation of EU law in Member States, EU Commission services are in a unique position to promote 3R approaches in regulatory compliance. Similarly, through their activities in international organisations and the regulatory dialogue with third countries, they can promote the 3Rs at a global level.

The European trade federations constitute the link between EPAA and the numerous companies not directly participating in the EPAA and its working groups, promoting the output of the EPAA across Europe:

Cefic, the European Chemical Industry Council

EFPIA, the European Federation of Pharmaceutical Industries and Associations

Colipa, the European Cosmetic Toiletry and Perfumery Association
EuropaBio, the European Association for Bioindustries
IFAH-Europe, the International Federation for Animal Health Europe
A.I.S.E., the International Association for Soaps, Detergents and Maintenance Products
ECPA , the European Crop Protection Association

The backbone of the EPAA is the direct participation of leading companies, actively committed to the promotion of the 3Rs. Today the EPAA has 35 companies. It is through direct participation of industry that EPAA membership extends beyond those participating on the Steering Committee or the EPAA Working Groups, acting as a *relais* between EPAA and those in their respective companies pursuing the promotion of 3R approaches. More than numbers, the active input and participation is relevant, and on a regular basis industry coordinates and assesses its members' contribution in the Partnership.

An updated list of EPAA members can be found on the EPAA website. [9]

Beyond the circle of EPAA partners, all those who are able to provide a valuable contribution to the pursuit of the 3Rs in regulatory compliance testing can participate in the EPAA working groups, subject to acceptance of the EPAA values and to criteria of efficiency. Several Working Groups therefore have representatives of NGOs and academia. Similarly, workshops organised by EPAA Working Groups are in principle open to participation by non-partners. Also the annual EPAA Conference attracts an increasing audience and participation of non-partners both in the EU and internationally.

Particular attention has to be paid to the Mirror Group, composed of relevant individuals drawn from among others academia, animal welfare associations, patient groups and consumer protection groups. Its role is to give an independent view on the Action Programme, the priorities, progress, and is a forum for the EPAA to seek comments on its activities from a broader societal perspective.

EPAA values and principles.

The EPAA values and principles[10] whilst being simple and straightforward, are highly important. They specify the scope of the EPAA mandate, covering not only replacement, but also reduction and refinement. They imply a major commitment from partners to make available human and financial resources to pursue the promotion of alternative approaches, and to contribute to the Action Programme. Similarly, they acknowledge that there is further potential for cooperation and sharing of knowledge between industry sectors, even if recognising that regulatory requirements of each industry sector are unique and that this will be reflected in the implementation of any deliverables.

They also constitute an invitation to stakeholders and interested parties to intensify jointly efforts to make available validated alternatives based on the 3Rs principles and to engage and contribute to the Partnership.

The EPAA stands for a science-based approach, bearing in mind the protection of intellectual property arising from innovation and the implications for the overall competitiveness of European industry. The development and use of alternative approaches to gradually change the way safety assessment is carried out will be based on past achievements from the different partners in applying the 3Rs. In pursuing their objectives, partners recognise the importance of the need to maintain a high level of consumer, patient, occupational, animal and environmental safety.

As a voluntary partnership, the EPAA works on the basis of consensus. As partners agree to work on the basis of a common set of principles and with a common vision, consensus is a powerful tool, reflecting the commitment of all partners involved.

In order to increase efficiency and output, the EPAA has opted to keep lean structures: a Steering Committee, responsible for the overall coordination; Working Groups, who are entirely responsible for the implementation of their work programmes, and a Mirror Group, creating a link to societal interests. Furthermore, the EPAA organises an annual Conference, presents an annual progress report, and is committed to a dynamic communication policy.

EPAA Achievements and Future Work.

The progress made in the first two years provides a thorough understanding of Europe wide activities in support of 3Rs and the barriers to their effective implementation. The initial premises on which the EPAA was based have been confirmed i.e. that significant scope exists to promote the application of the 3Rs:

1. through practical sharing of the experience, knowledge and technical know-how between the Partners, and across the industry sectors and Commission services
2. through the application of new, research led, science and technology which offer scope for completely new approaches to deriving the required safety information
3. by adopting a holistic approach to acceptance of alternatives, from validation and regulatory acceptance, harmonisation of global acceptance of new approaches and more effective dissemination of good practice to ensure widespread use and implementation.

On-line data bases have been developed and are available on the EPAA website containing (1) an inventory of ongoing research projects with the potential to deliver 3Rs benefits, projects evaluating optimised testing strategies and constituent elements across all relevant sectors (in cooperation with others as appropriate and (2) a review/inventory of existing (primarily industry in-house) 3R alternative methods and approaches employed in screening or decision making processes related to safety.

These databases constitute a basis for the development of practical processes and forums for active networking of knowledge and expertise, and allow for an identification of key cross sector opportunities for technology transfer and research.

Results so far are promising. In a 2005 Workshop, participants suggested that the one- generation Agricultural Chemical Safety Assessment (ACSA) approach for reproductive toxicity for plant protection products can be adapted for regulatory testing under REACH, replacing the two-generation reproductive toxicity testing. Work is ongoing between EPAA companies and ECVAM on validation of the revised ACSA protocol.

A High Level Workshop of eminent scientists, scheduled for April 2008, will advise on the research needed in order to enable future hazard identification (i.e. potential of exogenous chemicals or proteins to elicit adverse effects) with regards to chronic repeat dose systemic toxicity without the use of animal testing. The expected outcome is mainly new approaches that can be translated into new research areas that would deliver future alternative approaches in the safety assessment of chemicals and drugs.

Further work in the research area will concentrate on the potential for technology transfer and sharing across industry sectors, the implementation of the conclusions of the High Level Workshop, the identification of future policy drivers for safety testing as they relate to potential 3Rs initiatives, the extent to which research could mitigate the barriers to validation, regulatory acceptance and implementation.

Other priorities are the evaluation of opportunities for technology transfer such as study design optimisation (e.g., group sizes) in toxicological testing, recommendations for research on the inclusion of metabolizing systems into in vitro assays so that they are more capable of serving as definitive tests rather than preliminary screens, and the integration of the Research priorities within both the established FP7 (including related Technology Initiatives and Platforms) and industry processes to ensure appropriate science is funded and underway.

EPAA conducted a review of key national and European institutions with experience of 3Rs and, on the basis of representative case studies, evaluated factors that drive implementation of new 3Rs methods across boundaries/laboratories. This confirmed the extensive but highly fragmented nature of dissemination activities within Europe and the potential value of EPAA providing a single portal for accessing information on these activities. Most importantly the work identified a major gap in dissemination which relates to post validation implementation support for alternatives.

The EPAA will therefore further support the development of a single European portal to access information on 3Rs including recommendations for hosting this portal on a long term basis. It will also identify and seek to promote the necessary dissemination activities and processes which need to be in place post validation for efficient uptake of new 3R approaches.

Several workshops have been organised to obtain a better understanding of "hot spots" [11] for animal use and welfare in current and upcoming legislation and guidance documents, made available through reports on the EPAA website. A first analysis was made of drivers (e.g., safety, liability, precaution, risk acceptance etc.) for regulatory testing requirements in a number of sectors. Current and evolving practice and criteria for reporting of animal use have been assessed, and some recommendations made for improving implementation of the current rules, where appropriate.

As a follow-up, the EPAA will now concentrate on the implementation of a practical approach to facilitate sharing of regulatory experience across industry sectors which enables the consistency of cross-sector regulatory requirements to be assessed and thereby recommendations for 3Rs promotion to be made. A special focus will be given to the monitoring of the implementation of new regulations and the use of 3R methods within testing strategies (e.g. REACH/ITS; GHS). Case studies will be initiated to analyse consistency of implementation throughout sectors. Discussions take place with the European Food Safety Authority regarding the possibility to organise a joint workshop on the promotion of the 3Rs in the food and feed sectors. On a longer term, the EPAA will continue to identifiy and consider in a very pragmatic way appropriate (sector specific) measures to implement 3Rs in legislation and to avoid redundant testing of animals particularly in "*hot spots*".

More specifically in the area of validation and regulatory acceptance, the EPAA has identified (via agreed criteria) 24 priorities in the current ECVAM pipeline and made available to ECVAM information regarding data and substances that could help defined and prioritised validation studies.

The EPAA agreed on standard operating procedures in order to make the collaboration between validators and companies more efficient, including identification

of contact persons, guidance on the type of information that should be contained in information requests from validators and guidance to companies on processing validators' requests. If successful, EPAA will further promote this approach to other companies and sectors, which are not part of the partnership.

Dialogue within the partnership helped to identify a number of issues which are known to cause delay in validation procedure and which go beyond mere delays in providing information/substances. A detailed action plan involving all necessary stakeholders with implementation and monitoring mechanisms for the next 3 years of the Partnership is currently being designed.

A workshop on regulatory acceptance of 3Rs approaches (June 2007) allowed to identify potential barriers and reasons (scientific, administrative, political and legal) for delay of regulatory acceptance of alternatives. A number of concrete suggestions were made, relating to (1) a greater involvement of regulators at early stage of validation of a method, (2) better dissemination of information about alternatives available and organisation training in use, (3) regular cross-sectoral dialogue as the one initiated by EPAA and (4) international collaboration modelled on the ICH (International Conference on Harmonisation). Clear responsibility for different aspects, as well as boundaries of EPAA involvement, will be determined and agreed with relevant stakeholders.

On a more longer term, the EPAA will work on guidance on how and when to validate testing strategies (involving *in vivo* and/or *in vitro*/*in silico* methods as well as expert judgement) for safety assessment purposes (based on a case study approach) and work on a better understanding of regulators requirements vis-à-vis levels of confidence and acceptance of the validation of methods/ strategies. Finally the EPAA will seek to develop recommendations on 'alternative' processes to formal validation and an assessment of their applicability for different sectors.

Endnotes

1. Council Directive 86/609/EEC of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes.
2. Article 7
3. Treaty of Amsterdam amending the Treaty on European Union, the Treaties establishing the European Communities and related acts; Official Journal C 340, 10 November 1997.
4. Council Directive 76/768 of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products.
5. Directive 2003/15/EC of the European Parliament and of the Council of 27 February 2003 amending Council Directive 76/768/EEC on the approximation of the laws of the Member States relating to cosmetic products (Text with EEA relevance) ; Official Journal L 066, 11/03/2003 P. 0026 – 0035.
6. Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC,OJ L 396 of 30.12.2006.
7. COM(2006) 388 final 2006/0136 (COD) Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL concerning the placing of plant protection products on the market.
8. Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market1 provides for rules governing plant protection products and the active substances contained in those products.
9. http://ec.europa.eu/enterprise/epaa/partners.htm#com.
10. http://ec.europa.eu/enterprise/epaa/structure.htm
11. Priority areas for action that entail significant animal use and/or provide an opportunity for an effective impact on animal use through application of the 3R.