



The European Partnership
for Alternative Approaches to Animal Testing

2007 Annual Conference of the EPAA

European Partnership
for Alternative Approaches
to Animal Testing

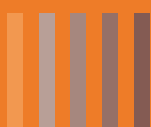
Report



The EPAA is a joint initiative from the European Commission and a number of companies and trade federations active in various industrial sectors. Launched on 7 November 2005, it aims to promote the development of new '3R' methods (based on the principles of Refinement, Reduction and Replacement) as modern alternative approaches to the use of animals in regulatory compliance.

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1 The report and its aim

This is the report of the third annual conference of the EPAA, the European Partnership for Alternative Approaches to Animal Testing, held in Brussels on 5 November 2007.

The EPAA's main theme for 2007 was regulatory acceptance of alternative approaches, and the Conference looked in detail at the hurdles that need to be overcome in this area but also at the progress that has been made so far.

This report seeks to highlight the main points that emerged during the Conference.

Progress achieved by EPAA throughout 2007 is presented in the appendix.

2 Introduction and key messages

The European desire to minimise the use of animals in safety testing is clearly stated and understood. Few aims could be simpler to define or more broadly supported - and yet at the same time be so complicated to address and so difficult to resolve. However, as the conference showed, progress is being made. As an example, work in the Netherlands was done to evaluate the added value of a second generation in a two-generation reproductive toxicity study. It confirmed the conclusions of the work conducted by ACSA¹ for crop protection products in the US, which aimed at reducing the need for the two-generation studies and extending the information obtained from the first generation. This approach has been one of the first identified by EPAA as having the potential to cut down animal use for the REACH² Regulation and to reduce testing costs.

But realising that potential is not simple. As Commissioner for Research Janez Potočnik explained in his keynote introduction, and subsequent speakers confirmed, the regulatory scene in Europe is a complex one - and for many sectors the regulatory scene is a global one, making things even more complex: "Separate national regulators exist in each country, in the broad sectors of chemicals, pesticides, pharmaceuticals, food, cosmetics, medical devices and biotechnology. Each sector is subject to a legislative regime with specific requirements in terms of animal testing. And each has varying degrees of European and international harmonisation that work on the basis of consensus." Potočnik - echoed by speaker after speaker - called for a "systematic and sustained exchange" between regulators, the research community and industry. There is a need, too, said MEP Dagmar Roth Behrend, chair of the EPAA Mirror Group, for more trust between the regulators and the public.

Above all, said Commissioner for Enterprise and Industry Günther Verheugen - and this was the general theme of the meeting - it is not sufficient to have validated alternative methods if the authorities in charge of implementation and enforcement do not accept them. Verheugen and just about every single speaker therefore called for greater involvement by authorities throughout the process, from validation to acceptance.

As Potočnik explained, "the urgency is mounting". From the start of 2009, animal testing for ingredients used in cosmetic products will no longer be possible. Marketing of cosmetic products will depend on availability of alternative methods. Companies urgently need validated alternative methods accepted by regulators. His warning was reinforced at the end of the meeting by Verheugen: "Nobody should have the hope or expectation that the deadlines will be changed," he said.

Presentations and discussion at the meeting were structured around three main themes, summarised in the three main sections of this report. The first was about drivers for regulatory acceptance and implementation. The last two dealt with the international dimension of 3R approaches: the issue of acceptance by the regulators and an examination of test cases.

The conference also heard that research will be the leading theme for EPAA in 2008. In this context, a workshop on new research avenues for "New Perspectives on Safety" will be held in Brussels on 28 and 29 April. The aim of this workshop, hosted by Commissioner Potočnik, is to generate new ideas on how to conduct research in order to assess systemic toxicity without using animals and in doing so help the EPAA to give input into up-coming research funding programmes, including Framework Programme 7.

¹ Agricultural Chemical Safety Assessment

² Registration, Evaluation, Authorisation and Restriction of Chemical substances.

Briefly summarised, the key messages were as follows:

1. The EPAA has emerged as a powerful platform enabling discussion among all stakeholders on the 3Rs, and although it can neither make nor enforce policy it can and does identify problems and solutions.
2. All stakeholders are committed to collaborating and ensuring that the vital requirement of scientific robustness for the alternative methods is met.
3. Commitment alone is not enough. The complex issues of promoting regulatory acceptance of alternative methods require structures for systematic and sustained dialogue and partnership throughout the whole process of research, development, validation and regulatory acceptance.
4. The European Commission must help actively to create these structures, including facilitating platforms related to the 3Rs. The European Parliament could also play a role in catalysing collaboration.
5. With products being produced and marketed globally, international harmonisation is essential. The European Commission has a vital role to play in stimulating global awareness throughout all sectors and in encouraging harmonisation, in particular, but not exclusively, with ICCVAM³ and JaCVAM⁴.
6. An urgent priority is to gain mutual recognition for assays that are accepted in different regions in order to avoid any additional testing.
7. All sources of information relating to safety testing and validation should be brought into a single portal for better accessibility and dissemination.
8. The various validators need to take part in effective dialogue, across industries and across jurisdictions. That dialogue could be aided by setting up, with European Commission support, an International Council of Validation Bodies.
9. Finally, we need to be ambitious but realistic. Time is short: we can and must do better.



Drivers for regulatory acceptance and implementation

What does it take to get a new testing method accepted by regulators? It is a simple question, but as often in this field the answers are not always to hand. However, a number of clear messages developed as the presentations and discussion unfolded.

If alternative strategies that meet the regulators' requirements are to be designed, it is essential first of all to understand what information is required from a test, how the information is used in each sector and what the potential is for a 3R approach. That should not be an ad hoc dialogue, as Odile de Silva (co-chair of EPAA's working group on validation and acceptance) from L'Oréal explained, but a structured discussion taking place across the various industrial sectors - "not a workshop once in a while".

Decisions must be taken on the basis of methods that are scientifically robust: the key driver for acceptance, said de Silva. Once a new method is established, information about it needs to be provided in a more efficient and coordinated way, which means better dissemination. And there needs to be dialogue and discussion on how the new method fulfils the regulators' needs. That dialogue should be carried over into post-marketing monitoring and revision, so that the method can be refined and improved.

Therefore, regulators and industry should consult with each other, and be consulted, at every stage in the development of alternative methods and testing strategies - a proposal echoed by Jean-Marc Vidal from the EMEA⁵ and Betty Hakkert from the RIVM⁶.

Professor Marcel Leist, from the University of Konstanz, Germany, agreed: early involvement of regulators speeds up the whole process, and leads to a build-up of confidence and experience that can be applied elsewhere. Leist explained how important constant feedback is during the whole development of a testing method. But, he added, "there are very few institutions and mechanisms to ensure that feedback". The only institution that has taken on a catalysing role is ECVAM⁷ but, he said, "It needs to take on a larger role".

³ US Interagency Coordination Committee on the Validation of Alternative Methods

⁴ Japanese Centre for the Validation of Alternative Methods

⁵ European Medicines Agency

⁶ Dutch National Institute for Public Health and the Environment

⁷ European Centre for the Validation of Alternative Methods

EU regulation increasingly contains provisions on alternative approaches, creating incentives and new “paths” towards alternative approaches as was described by Patricia Brunko from the European Commission’s DG Health and Consumer Protection, who presented the proposal for a Regulation replacing Directive 91/414/EEC on Plant Protection Products. This regulation prohibits duplicative testing, requires promotion of alternatives and introduces a tiered approach.

David Grant Lawrence from the European Commission’s DG Environment, explained that new accepted alternative methods would be introduced into the Commission’s new Test Methods Regulation. However REACH opens two other avenues that should be further explored: there may be sufficient weight of evidence either from the use of new test methods not yet included in the Regulation, or from a method approved elsewhere but not yet recognised by the Commission. On that basis it can be concluded that a substance does not have a particular dangerous property.

Once a successful alternative approach has been developed, as Julia Scheel (co-chair of EPAA’s Working Group on 3Rs in regulation) from Henkel explained, it needs to be disseminated, and researchers and other potential users need to be trained to use it. That, she said, raised the question of whether to set up official training centres for 3R methods. There are none currently. And as Commissioner Potočnik pointed out, there are only four professorships in alternative testing in the whole of the European Union.

The quality and accessibility of information remain hurdles to be overcome. The EPAA has created two valuable databases that hold information on, respectively, current industry approaches and all national and EU research projects with the potential to contribute to the 3Rs. But more is needed. For example, it is easy to find OECD⁸ protocols, but other methods may have been used in specific contexts and be less accessible. Many organisations are working to provide such information, but sometimes in isolation. A potential solution that Scheel said EPAA has identified is to bring all the sources of information together into a single portal.

4

The international dimension of 3R approaches - acceptance

Industry operates in a global environment. Its products are often marketed all over the world. But to do this industry needs to satisfy multiple authorities relying on different methodologies, and with different demands for safety testing.

The afternoon session of the meeting was mainly dedicated to this topic, but in fact it came up in presentations and discussion throughout the day. One of the first conclusions to emerge, repeated by speaker after speaker, was the need for action internationally.

Odile de Silva explained that the research, development, validation and use of alternative approaches make sense only if accepted by regulatory authorities worldwide. It does not help any stakeholder, as Gunnar Riemann from Bayer said, if we have alternative methods in Europe but still have to do animal testing for other regions.

From BASF, Hennie Kamp (co-chair of EPAA’s working group on research) also criticised the duplication and waste of effort that result from different regions wanting different tests. An example: the Local Lymph Node Assay, which is accepted in the European Union and the United States, but with different numbers of animals. To complicate matters further, the test is not accepted in the US for agrochemical formulations. And, said Kamp, this is not just a transatlantic issue: “Often the position in, say, Japan and Brazil is unclear or the same as in the US.”

Much is being done already, but much more remains to be accomplished. Georgette Lalis from European Commission’s DG Enterprise and Industry, and co-chair of EPAA’s Steering Committee explained that amongst other initiatives, alternative approaches are a standing point on the agenda of dialogue with trade partners. She pointed out differences in approaches to validation in different regions, which may hinder acceptance and mutual recognition. Hence, for the sake of harmonisation, she suggested to set up an International Council of Validation Bodies.

For industry, Bayer’s Gunnar Riemann said that one priority was to align industry needs and Commission priorities, to bring realism to the debate on alternatives. He stressed the need to focus on implementing “tangible actions” and on involving international regulators even more.

⁸ Organisation for Economic Co-operation and Development

In the US, as presented by Abigail Jacobs from the FDA⁹, all regulatory agencies, as members of ICCVAM, take part in the working groups evaluating ICCVAM alternative test methods, together with US research agencies (which is not the case in Europe). ICCVAM acceptance criteria fit into the regulatory testing structure, and are used as guidance by regulatory agencies for acceptance decisions. But formal validation is not always required in all sectors before regulatory acceptance. As long as scientific quality of the method is demonstrated, some flexibility can be applied.

Betty Hakkert insisted on the need for regulators to be involved throughout the development and validation process, on better transparency and on cross-sectoral dialogue as well as on mutual acceptance of data within the EU and internationally.

Vice President Verheugen expressed that the Partnership is only one instrument amongst others in pursuing the realisation of our objectives and that it has its limits. Issues identified in the framework of the European Partnership may have to be taken up for further action by the relevant competent authorities, or by industry itself.



The international dimension of 3R approaches - test cases

The hurdles faced by any company selling its products globally were starkly illustrated by two case studies: one from industry and one from the area of research.

Ann De Smedt from Johnson & Johnson explained how testing guidelines for phototoxicity - where, following exposure to a chemical, the skin reacts adversely to light - varied between the European Union and the United States. In Europe, *in vitro* testing is encouraged; the US FDA requires testing in animals. And so, of course, Johnson & Johnson is obliged to perform both.

But De Smedt also explained that the *in vitro* test is not perfect, and has a high rate of false positives. Johnson & Johnson's approach therefore is to use it first: if the *in vitro* test result is negative, it does not test further; if positive, the compound is subsequently tested in animals.

Thomas Montag from Germany's Federal Agency for Sera and Vaccines, based at the Paul Ehrlich Institut, looked at another testing area - pyrogenicity. It is a serious concern: depending on the concentration of a pyrogen (and its ability to induce fever), the adverse reactions can be life threatening. Current testing for pyrogens is carried out in rabbits or by using lysate prepared from blood of horseshoe crabs, but a new test method using blood samples, without animals, has been developed and validated. This method is at least as valid as working with rabbits, and agencies in Europe and the United States are currently assessing it via ICCVAM. Progress is however slow despite the fact that authorities in both regions are interested in the method.

Japan, meanwhile, is starting a peer review of alternative pyrogen tests in 2008.

The lesson here is that the development and the validation of an alternative method is greatly improved when regulators are involved from the very beginning. Yet even then progress can be slow, and requires structured discussion and feedback.

⁹ Food and Drug Administration

Appendix 1: The background - 2007 achievements

The EPAA has increasingly made its presence felt on European and global levels, explained Charles Laroche, co-Chair of the EPAA Steering Committee, from Unilever. Key developments have been:

1. Creation of databases

The EPAA has established a comprehensive overview of the state of play, with two databases now set up and accessible via a dedicated website. The first looks at current industry 3R approaches, and is a tool to share information and strategies that might be transferred and applied within and between sectors. The second identifies all the national and EU research projects with the potential to contribute to the 3Rs.

These databases help the EPAA to assess the possibility of replicating 3R methods between sectors and identify research opportunities to provide new and creative approaches for effective safety assessment.

2. Identification of research priorities

Priority research areas identified so far include systemic toxicity (see Workshop planned in April 2008 as mentioned on page 3) and overcoming the inability - or at least low ability - of in vitro testing systems to metabolise xenobiotics. The latter is a serious scientific limitation and one of the obstacles for in vitro approaches gaining acceptance.

A second area is testing for reproductive and developmental toxicity, a particularly challenging requirement under the REACH Regulation, which governs how chemicals can be used. An EPAA workshop held in November 2006 led to a task force being set up under the aegis of ECETOC¹⁰ which is due to report soon. The EPAA is contributing to facilitate this process.

Before a new method can be used in support of regulation, it has to be scientifically validated and then accepted by authorities for regulatory purposes. "It is a lengthy process, invariably, and so we are working on ways to shorten it," Laroche told the meeting, "to speed things up without jeopardising the quality of the scientific work."

In the past, the emphasis has been on identifying and overcoming sector-specific issues for chemicals, pharmaceuticals, agrochemicals and cosmetics. The EPAA focus is to look for cross-sectoral lessons and then apply them.

3. Facilitation of dialogue with the validators

The EPAA has great potential to do something - and quickly - about one of the main obstacles to progress, by opening up access to existing data and facilitating communications between industry and validators such as ECVAM. It has already identified 24 alternative methods for support by member companies, developed guidance for validators on formulating information requests and for companies on responding to the requests.

Another challenge is to ensure that validated alternative approaches are accepted by the authorities in the regulatory compliance framework. In June, the EPAA held a workshop with a wide range of stakeholders, to explore potential barriers and reasons for delay in regulatory acceptance of alternative approaches. Several recommendations were made, which are currently being implemented at various levels.

4. Mapped: dissemination of information on the 3Rs

The EPAA has been studying how they spread information and promote the 3Rs, culminating in a workshop in October 2007 looking at how dissemination strategies influence the uptake of new 3R methods. The major problem identified was the lack of a systematic process to ensure widespread uptake, acceptance and implementation of new 3R methods post-validation. The success so far has been due to the commitment of personal champions, which is not an efficient process for the future.

5. Measuring the uptake

The EPAA's work with experts in statistical reporting has shown that statistics simply do not work well enough to measure the uptake of 3Rs in regulatory testing; there are too many variables. So the Partnership is in the process of looking at other ways to measure uptake.

6. Reaching out

Lastly, the EPAA has been active in outreach and interaction with stakeholders via the Mirror Group and directly with the likes of the European Parliament and SCCP¹¹.

¹⁰ European Centre for Ecotoxicology and Toxicology of Chemicals

¹¹ Scientific Committee for Consumer Products

This report was prepared for the EPAA by Peter Wrobel, Journalist, in collaboration with EPAA Working Group 5 on validation and acceptance.

The EPAA Progress Report of 2007 is available at www.epaa.eu.com.

