



# **The European Partnership for Alternative Approaches to Animal Testing**

**Symposium "20th Anniversary of ZEBET at BfR",  
October 26 -27, 2009**

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L'Oréal  
Industry co-chair**



## An innovative and dynamic approach

A partnership between industry and authorities committed to the 3Rs, joining forces for the promotion of alternatives in regulatory testing:

- Services of the European Commission
- European trade federations, covering 7 sectors
- Individual companies, currently 39 in number

Open for participation by industry sectors and companies committed to the 3Rs and willing to share expertise

The logo for the European Partnership for Alternatives to Animal Testing (EPAA). It features the lowercase letters 'epaa' in a white, cursive, handwritten-style font, positioned on the right side of a wide, horizontal orange-to-yellow gradient bar that spans the bottom of the slide.

# The Partners

## ➤ **Services of the European Commission**

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

## ➤ **Federations**

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

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# The Partners

## Companies

Abbott  
Astra Zeneca  
Avon  
BASF  
Bayer  
Beiersdorf  
Boehringer Ingelheim  
Chanel  
Colgate-Palmolive  
Dow  
DSM  
Elizabeth Arden  
Estée Lauder  
Euroderm

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  
StratiCELL  
Syngenta  
Unilever

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## EPAA Principles and Values

- Science based improvement in implementation of 3Rs
- Consensus based approach between industry and authorities
- Pragmatic mechanisms and a workable structure
- Dialogue and transparency towards stakeholders and interested parties in particular through a Mirror Group
- Commitment of partners to act in a coherent and consistent way

The logo for EPAA (European Partnership for Air Quality Assessment) is located in the bottom right corner. It features the lowercase letters "epaa" in a white, cursive script font, set against a background of a horizontal gradient bar that transitions from orange on the left to yellow on the right.

## Main areas of EPAA activities

- How to get the best out of Research
- Assessment of relevance legal requirements and implementation
- Streamlining Validation and Acceptance
- Improving Information and Dissemination

## Some representative EPAA projects

- EPAA databases for in house methods and publicly funded R&D projects
- **Evaluate opportunities across all sectors for an extended one-generation study for reproductive toxicity**
- Framework for cooperation on validation
- Regulatory dialogue: e.g. ICATM and OECD
- **Paving the way towards new perspectives on safety**
- In vitro metabolism test systems as essential part of ITS for long term toxicities
- **Acute toxicity testing across sectors**
- EPAA annual lead themes, e.g. 2009 **Dissemination**
- **New initiatives, e.g. ITS**, ADME, vaccines, weight of evidence

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## Evaluate opportunities across sectors for an extended one-generation study for reproductive toxicity

- EPAA discussed in detail and agreed that the extended one-generation study as developed by the ACSA project could, in principle, be applicable to safety testing under REACH and replace the two-generation study (OECD 416).
- It was agreed in discussions with all stakeholders that the complex ACSA protocol could be modified in order to meet the current requirements for industrial chemical safety testing.
- This will deliver animal welfare benefits with regard to both refinement and a reduction in the number of animals used (more than 40% compared to the two-generation study).
- An ECETOC task force has developed an approach, where the components of the protocol could be used as modules for use under REACH to design reliable triggering and/or waiving criteria. This was published in ATLA 37(2), 219 (April 2009)



## Current status

- Feasibility of the ACSA extended one-generation study protocol has been evaluated by **four EPAA member companies**
- First results with model compounds have been presented by some of the industry partners (BASF) while other member companies of the EPAA (Bayer, Dow, Syngenta) are currently finalizing their studies/ evaluations.
- An OECD expert group was set up end of 2007 to develop a draft guideline and evaluate the validity of the endpoints used. This draft OECD guideline is still under discussion.
- EPAA will support a workshop with ECPA in Q2 2010 to disseminate the latest results to the stakeholders.

The logo for the European Partnership for Assessment of the Chemical Safety of New Active Substances (EPAA). It features the lowercase letters 'epaa' in a white, cursive, handwritten-style font, positioned on the right side of a wide, horizontal orange-to-yellow gradient bar that spans the bottom of the slide.

## Acute Toxicity

The requirement for acute toxicity within the pharmaceutical sector has been successfully challenged\*. This led to the idea to investigate requirements and 3Rs possibilities in other sectors

- \*- Regulat. Toxicol. Pharmacol. 2008; 50, 345-352
- ICH M3 R2, Recommended for adoption, 11 June 2009

## Acute Toxicity and EPAA

EPAA identified opportunities to be proactive & analyse scientific/regulatory drivers across sectors & make recommendations on what is possible or not possible in different sectors based on the regulatory needs of the respective sector

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## Acute Toxicity and EPAA

- A 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 sponsor a workshop in February 2010 to discuss with regulatory authorities specific proposals for waivers that would deliver direct 3Rs benefits.

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## Acute Toxicity and EPAA

- An EPAA survey on the drivers and methodology of acute toxicity tests in different sectors obtained a response from 18 companies (non –pharma)
- An EPAA paper will be submitted for publication in 2009.
- The survey revealed that the key driver is classification and labelling.
- Most companies confirmed that they would be ready to skip the dermal testing route if a robust set of data supported the possibility.
- an in-depth regulatory dialogue, within and across sectors, is necessary to implement the 3Rs and to take account of the complexity of the regulatory landscape.

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## *New perspectives on safety*

**EPAA members are convinced that cutting-edge research will pave the way to the accelerated development of alternative approaches to assure safety**

- **The goals of the 2008 workshop were:**
  - To identify truly novel approaches for the characterization of the potential hazards of chemicals and drugs.
  - To develop a view of which areas of science and technology should be exploited to create new approaches to safety assessment, and of which activities may inform and shape the forward research agenda.
  - To invest in alternatives research a greater legitimacy among the scientific community
- **Some key areas for future exploration were identified:**
  - stem cells
  - toxicogenomics
  - computational chemistry/cheminformatics
  - bioengineering
  - systems biology
- **EPAA decided to focus activities on stem cells and computational chemistry**

The logo for EPAA (European Partnership for Alternative Approaches) is a stylized, handwritten-style script of the letters 'epaa' in white, set against a background of a gradient bar transitioning from orange to yellow.

# *New perspectives on safety*

## Expert panel

<b>Prof. Sir Colin Berry,</b>	College Gardens Dulwich London, UK
<b>Prof. Pierre Chambon,</b>	Institut de Genetique et de Biologie Moleculaire et Cellulaire, France
<b>Prof. David Eaton,</b>	University of Washington, Dpt of Environmental and Occupational Health Sciences, USA
<b>Prof. Decio L. Eizirik,</b>	Laboratory of Experimental Medicine Universite Libre de Bruxelles (ULB), Belgium
<b>Prof. Jay Goodman</b>	Michigan State University Department of Pharmacology and Toxicology, USA
<b>Prof. Jan-Ake Gustafsson</b>	Dpt of Biosciences and Nutrition Karolinska Institute, Sweden
<b>Prof. Hans Lehrach</b>	Max Planck Institute for Molecular Genetics Berlin, Germany
<b>Prof. Barry Marshall</b>	The Office of the Nobel Laureates Perth, Australia
<b>Prof. Sten Orrenius</b>	Karolinska Institute Stockholm, Sweden
<b>Prof. Roger Pedersen</b>	University of Cambridge School of Clinical Medicine Cambridge, UK
<b>Prof. W. Graham Richards</b>	University of Oxford, Central Chemistry Laboratory Oxford, UK
<b>Prof. Nancy J. Rothwell</b>	Faculty of Life Sciences University of Manchester, UK
<b>Prof. Anthony P F Turner</b>	Distinguished Professor of Biotechnology, Cranfield University, UK

A stylized, handwritten-style logo in white, possibly representing the word 'epan' or a similar name, set against a solid orange background.

## COMPUTATIONAL CHEMISTRY POTENTIAL

- Computational chemistry is rapidly becoming more powerful, quicker, faster and today has almost unlimited power that is being used in very creative ways outside of the field of toxicology.
- Can we harness some of these technological advances in chemistry to start to look at toxicological problems in a completely different way?
- It is possible to envisage the modelling of virtual cells and even organs.
- An opportunity to increase collaborations between chemists and toxicologists to broaden the impact of chemistry from a role in studying correlations with biological effects.

The logo for the European Partnership for Advanced Assessment (epaa) is located in the bottom right corner. It features the lowercase letters "epaa" in a white, cursive, handwritten-style font, set against a background of a horizontal gradient bar that transitions from orange on the left to yellow on the right.



## Computational chemistry and toxicology

- A case study will be used to focus the initial discussion. The interaction of chemicals with the liver will be used to think through what the research blocks would look like towards an ultimate goal of predicting adverse hepatic effects that may occur in man on exposure to a novel molecule.
- A specific activity to widen the types of scientists involved in such a discussion would need to be the first step and include scientists such as chemists, cheminformaticians, scientists with knowledge of the liver and modellers familiar with systems approaches.
- A project team of EPAA has started on May 5th with the organisation of a workshop on this topic
- The workshop is currently scheduled for the first half of 2010

# Stem cells

- EPAA assessed that the current research on the use of stem cells would benefit from a discussion on how, if this work is ultimately successful, it would align with industry needs for safety assessment without animals (e.g. the needs of REACH, 7<sup>th</sup> Amendment to the Cosmetics Directive etc)
- The identification of gaps in testing strategies is relevant in order to select the cell type of interest as well as the most appropriate readout to identify relevant mode of actions.
- The following information could be of help for a focussed test development:
  - Which cell types have priority for the development of differentiation protocols?
  - Which readouts are of interest?
  - List of reference compounds mimicking the most relevant mode of actions
  - Ensure that in the planned FP 7 call findings of existing projects are taken into account in order to avoid duplication of work.

## Stem cells

- The perspectives offered by stem cells in different life sciences application fields have originated several projects (18 projects on human stem cells financed under FP6 and FP7). Only four FP 6 projects are using hESC for the development of toxicity tests
- Based on this background, EPAA recommended a meeting with involved scientists and representatives from the 7 sectors to discuss possible priorities for FP7-funded stem cell research
- A first expert meeting has taken place in October this year

# *New perspectives on safety*

## *Next steps*

1. Progress with 2 specific outputs from the New Perspectives on Safety workshop
  - Chemistry and toxicology – case study: liver
  - Stem cells
2. Engage scientists from international groups previously unconnected with 'alternatives' in the scientific challenges we face
3. Consider how these two themes could align with overall challenge of assessing chronic repeat dose systemic toxicity without the use of animal testing

The Commission /Colipa Joint Initiative (FP7 call – 50Mios €) is already building on the EPAA initiative.

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# The European Partnership for Alternative Approaches to Animal Testing

'Validation of Integrated Testing Strategies'

2<sup>nd</sup> Workshop – 12<sup>th</sup>-13<sup>th</sup> Oct 2009

## Objectives

- Discuss to which extent the existing validation principles are applicable to validation of testing strategies (based on selected case studies)
- Develop a draft approach for validation of ITS and apply it to the selected case studies

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## Recommendations of the workshop

- Assessment of the building blocks
  - Test needs to be reliable and biologically relevant
  - Predictive capacity of each building block is not as important
  - Building blocks will be integrated via a testing strategy
- Is there added value in validation of a testing strategy?
  - Integrated Testing Strategy (i.e. Weight of Evidence approach) can not be validated
  - Testing strategy for replacement – can be validated, do we need this?

# Recommendations of the workshop

- Evaluation of an individual *in vitro* test method to qualify it as a building block would involve at least the first 4 modules of validation:
  - Test definition; Within-lab variability; Transferability; Between-lab variability
- In addition,
  - The biological relevance of the parameter of interest would need to be established
  - The chemical selection fits the biological relevance
  - The ability to measure the parameter of interest (not endpoint) would have to be assessed

# Recommendations of the workshop

## Follow-up:

- EPAA workshop report – Q4 2009
- EPAA WG5 workshop – Q2 2010 – *Regulatory Acceptance of Testing Strategies (t.b.c)*
  - Industry testing strategies case studies
  - ECVAM validation rationale for building blocks and testing strategies for 3Rs
  - Regulators (including international regulators) to pro-actively attend and comment



# EPAA Information

http://ec.europa.eu/enterprise/epaa/index\_en.htm

Document sans nom X What We Do

**The European Partnership for Alternative Approaches to Animal Testing**

Home About EPAA Governance Activities Events News Contact

**EPAA: A joint initiative**



The European Partnership  
for Alternative Approaches to Animal Testing

Nobody likes animal testing. That is why many millions of euro have been devoted to research into alternative ways to assess safety. Already this investment has produced some important results, and made it possible to reduce the number of animals used in meeting legally-required tests. But in certain cases the only way at present to understand the safety risks posed by medicines, consumer goods, chemicals or pesticides is to conduct tests that use animals. So more research - and better co-ordinated research - is still needed to continue refining, reducing and replacing animal use.

To boost this coordinated research effort, the European Partnership on Alternative Approaches to Animal Testing (EPAA) was launched in November 2005 by European President Günter Verheugen and Science & Research Commissioner Janez Potočnik.

The EPAA is an unprecedented collaboration between the European Commission and companies from seven industry sectors. The partners are committed to pooling research and resources to accelerate the development, validation and implementation of alternative approaches over an initial five-year period.

[The Three Rs Declaration - EPAA Potential and Benefits - An Action Programme for EPAA Members](#)

**Highlights of EPAA activities**

The partnership focuses on mapping existing research, developing new alternative approaches, and promoting communication, education, validation and implementation of alternative approaches. Some of the principal current activities are:

- Exploring the use of an extended one-generation study to replace the study required by REACH. Four companies are checking the feasibility of which has a huge **reduction** potential. [More](#)
- An *in vitro* metabolism project addresses one of the greatest unmet challenges in replacement. Methods used in different sectors/companies are being optimized to accelerate the development, validation and implementation of replacement. [More](#)
- For systemic toxicity testing, in addition to optimizing currently used approaches, EPAA also examines research opportunities to develop innovative approaches. Outcomes of the scientific workshop that took place in 2006 in participation of scientists representing the cutting edge of different sectors are further explored. [More](#)

**Highlights**

EPAA Annual Conference 2009  
"Dissemination"

Brussels, November 6th, 2009,  
Charlemagne Building  
(Programme available soon)

**OVERCOMING BARRIERS TO VALIDATION**

From research to implementation

March 2009

## Contents

- Dissemination of good practice
- Launch of a new EPAA website
- EPAA workshops on *in-vitro* metabolism and Integrated Testing Strategies – the challenges ahead



## EUROGUIDE

On the implementation and use of scientific methods for the assessment of safety and other scientific purposes

Based on the advice provided in the European Commission's 2005/2006

The Council of Europe is the continent's oldest political organization, founded to ensure the development of Europe's political, economic and social progress. It has been a pioneer in the development of scientific methods and the implementation of other scientific purposes. It has been a pioneer in the development of scientific methods and the implementation of other scientific purposes. It has been a pioneer in the development of scientific methods and the implementation of other scientific purposes.

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## Dissemination of Good Practice

In December 2006, after 10-year technical and scientific expert debates, the review of Appendix A with housing and care standards was completed and adopted by the Council of Europe.



## Why is Dissemination Important for the Partnership?

- Dissemination of information about existing replacement, reduction and refinement methods is one of the conditions for
  - better implementation of 3Rs and
  - better acceptance by regulatory authorities.

## Two Step Process Agreed

- Step 1: To explore with target audiences their information needs and - on this basis - to identify the most effective tool for dissemination of 3Rs information
- Step 2: To develop the most adequate dissemination tool with the help of experts in the field

# Mechanism of Dissemination Questions

- Who are the target groups/audiences that could benefit from an EPAA-led dissemination tool on the 3Rs?
- What do these target groups need to know about the 3Rs?
- Are they able to obtain the information they need from other sources and, if so, how easy is the accessibility?
- Could the target groups benefit from information on the 3Rs that they do not currently search for or have access to?
- If there is a significant unmet need for effective dissemination of 3Rs information, is EPAA likely to be able to make a significant impact?
- If so, what would be the best mechanism for achieving this positive impact in 3Rs dissemination?

# 2009

## The year of Dissemination

**EPAA Annual Conference**  
**Brussels, November 6th,**  
**2009**

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