The European Partnership for Alternative Approaches to Animal Testing

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Odile de Silva
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 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)

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

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

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

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.

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

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.

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.

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**

New perspectives on safety

Expert panel

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

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.

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, 7th 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 Intitiative (FP7 call – 50Mios €) is already building on the EPAA initiative.

The European Partnership for Alternative Approaches to Animal Testing

'Validation of Integrated Testing Strategies'

2nd Workshop – 12th-13th 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

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 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

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