

The European Partnership for Alternative Approaches to Animal Testing

Alternative Test Methods Session
of the 5th Meeting of Chairs and Secretariats of EU Commission and
Agency Scientific Committees and Panels involved in
Risk Assessment. Brussels 19 November 2009

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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

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 acceptance
- 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. Validation of ITS, vaccines, weight of evidence



ACSA extended one-generation study

Developed in the crop-protection context.

<u>Status</u> of feasibility evaluation for chemicals:

- Evaluation by four EPAA member companies: 2 are currently finalizing their studies / evaluations
- An OECD draft guideline is open for comments, including triggering criteria, however there is some reluctance to accept it without assessment of all cohorts.
- EPAA will support a workshop with ECPA in 2010 to disseminate the latest results to the stakeholders



Acute toxicity

- The requirement for acute toxicity within the pharmaceutical sector has been successfully challenged
- EPAA is reviewing drivers for this test to identify 3Rs opportunities for all sectors

Status

- Publication on drivers for acute tox testing across sectors in 2009
- Opportunities for waiving one of the three routes of administration
 - Two separate but complementary retrospective data analyses conducted by ECVAM/HSI and the UK NC3Rs
 - EPAA Workshop with regulators to discuss findings in early 2010



New perspectives on safety

Workshop in 2008:

- To identify truly novel non-animal 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.



New perspectives on safety Next steps

- 1. Progress with 2 specific outputs from the New Perspectives on Safety workshop
 - Computational 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.





Skin Sensitisation Risk Assessment

Risk? Hazard Exposure





Product

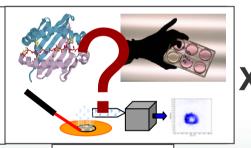




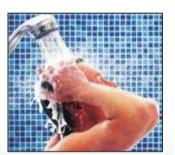
Historical



In Silico

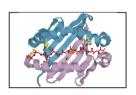


In Vitro





How can we characterise sensitiser potency without animal testing?



Identify the key parameters involved in skin sensitisation induction



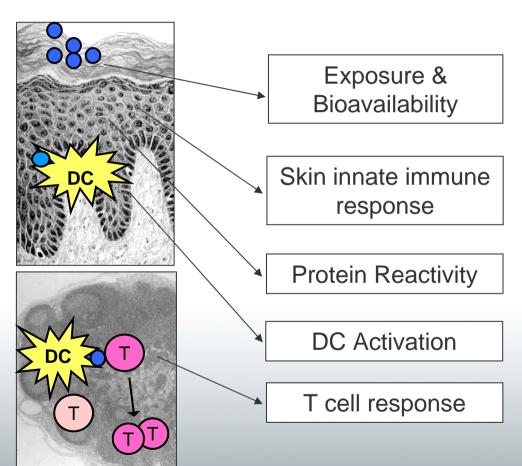
 Develop non-animal test methods that aim to model each key parameters



 Integrate data from different test methods to predict sensitiser potency information



Testing strategies for the prediction of skin sensitisation potency information



J. Appl. Sectors. 2006; 26: 341–254 Published colline 15 June 2006 in Wiley Investment

InterScience

A future approach to measuring relative skin sensitising potency: a proposal

ian R. Jovesey, ** David A. Basketter, * Carl Westmoreland* and Ian Simber*

 Unificar Salaty and Festimannia (Asserting Centre, Colore II) House, Standards, Sulfandistra, MSSS 110, U.S.
 Symptotic Central Institutions Internations, Although Park, Mandards II, Charles, MCD 411, US. Realised IT Sensory 2006; Revland 22 Frincery 2006; Accepted 29 February 2006.

ABSTRACT: Current approaches to skin sensitivities with assessment are dependent a pan the availability of information regarding the fundamental parameter. For firstly, data relating to the whiche skin sensitiving opiniony of the chemical, and sensitivity, information requiring likely conditions of human expanses. During the part two detailes, much be similar experiments of the conditions of human expanses. During the part two detailes, much be similar. additived in terms of refining methods capable of informing those parameters. For example, the development of the head lyingth node once; (LLNA) has made if possible to provide this sound sing housed, and to determine relative this contribility potancy, is a sery hat was not possible provincely. Taken together with accounting their problems exposure, such privacy data can be used in the determine the devication of effective risk assessments. However, although required, we appropriate an integrated consequence of relation controlling material, for the recognition that we described an integrated consequence of relation controlling material, for their recognition that we described animals of the following materials of the recognition of dends provided an understanding of the sarious biological, historiemical and chemical factors that impact on the allerges properties of chemicals and the completion of skin complication, and an ability to measure these in rate. Copyright © 200

KITY WORTE: skin; sensitivation; allegg; in visco; in skin;

Skin Sensitisation

Allergic centure demotitis (ACD) resulting from skin sensitivation is a simplicant environmental and occupational health concern. Consequently, there exists a continuing and important need to identify accessely chemicals that have the potential to cause skin sensition on (Stelling at a', 2001; Kimber at al., 2002). In common with other types of allergic disease, contact allergy develops in two temporally discrete places. During the first of these, the 'Induction' phase, topical exposure of an inherently associated individual to an appropriate and sufficient asserts of a skin terrsitiving chemical senats in a crimary extensors immune resource characterised by the closed expansion of allergen-specific T lymphocytes in draining tyoph under, Al this point semilisation has been aparited. The expanded persulation of allegenreactive T lymphocytes distribute systemically such that subsequent recounter of the reactived subject, at the same or a different skin site, triggers as accelerated and

* Correspondence for Lie S. Jovey. Digitive Subsysted in encomments becomes Corre. Colocci. Name, Specifical, Published Miller HD, UK.

Copyright in 1986 July Why & Son, Lab

The question is frequently posed about the characteristics that couries on characteristic the shiftly to cause the acquisition of this territorion. Periops the more helpful perspective in tackling this issue is to define the hurdles a chemical must regotive successfully in order to cause skin sensitisation. The key properties required for suc-conful skin americanism can be summarised as follows: (a) the shifty to gain across to the visible epidemic via the abuses convene, (ii) the principal to from stable conjugates with protein to create an immunocental matery (c) the characteristics required to cause the expression or increased expression, of those this cytokines that are known to be necessary for the induction of conneces immune responses, and (d) inherent fireignness, or the degree of incremagenicity required to provoke a cutage tes T lyanginossis response of the magnitude nor for the acquisition of skin sensitivation. Each of those characteristics is now considered briefly:

that causes derived inflammation recognized circically as allowic contact dematkle. This is known as the

Jowsey et al. 2006. J. App. Toxicol. 26. 341-350.



Evaluating *in vitro* test methods for Skin Sensitisation



- Three in vitro test methods accepted for ECVAM phase III pre-validation:
 - Direct Peptide Reactivity Assay (DPRA)
 - Human Cell Line Activation Test (h-CLAT)
 - Myeloid U937 Skin Sensitisation Test (MUSST)
- Each test had previously undergone in-house and interlaboratory evaluation to:
 - Optimise and fix protocol
 - Evaluate protocol transferability
 - Characterise accuracy of prediction
 - Define applicability domain



Integrated Testing Strategies in the regulatory context

- Two workshops: November 2008 and October 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

Status

- Agreement on the assessment of the building blocks which will be integrated via a testing strategy
- Is there added value in validation of a testing strategy?
- Recommendation for a 3rd EPAA Workshop Q2 2010 Regulatory Acceptance of Testing Strategies



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.



Conclusions

- Provide appropriate answers to regulatory & safety requirements, bringing together advanced scientific approaches and the 3Rs
- Help the dialogue between industry, academia and regulators in order to facilitate the international implementation of these approaches
- Improve our efficiency by adapting our working processes and facilitating interactions with our stakeholders with the help of the Mirror Group.



This paper was produced for a meeting organized by Health & Consumers DG and represents the views of its author on the subject. These views have not been adopted or in any way approved by the Commission and should not be relied upon as a statement of the Commission's or Health & Consumers DG's views. The European Commission does not guarantee the accuracy of the data included in this paper, nor does it accept responsibility for any use made thereof.