Development and use of Integrated Testing Strategy for skin sensitization under REACH

Dr Kimmo Louekari
Senior Scientific Officer, ECHA

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Allergic contact dermatitis

- “Thousands of different products may cause skin sensitisation, including antioxidants, preservatives, antiseptics, biocides, pesticides, disinfectants and cleaning agents, metals, constituents of plastic and rubber materials, oils, pigments and dyes, cosmetics, rosin, turpentine, plant (latex) and animal proteins and enzymes.”


- “Chromates, epoxy resins and their hardening agents, acrylic resins, formaldehyde, formaldehyde releasers and formaldehyde resins, biocides, hardwoods, are common examples as well as rubber latex, cutting oils and hexavalent chromium” (HSE Guidance Note MS 24. 2004).

- There are tens of thousands occupational allergic contact dermatitis annually. Significant part of these is caused by chemical exposures. In addition, consumers may develop skin sensitization after exposure to chemicals.
Information requirement for Skin sensitisation, Annex VII of REACH, above 1 tpa

- LLNA is the first-choice method for *in vivo* testing. Only in exceptional circumstances should another test be used. Justification for the use of another test shall be provided.

- In vivo test is not necessary
  - if the available information indicates that the substance should be classified for skin sensitisation or corrosivity; or
  - the substance is a strong acid (pH < 2.0) or base (pH > 11.5); or
  - the substance is flammable in air at room temperature.

Before *in vivo* test, the registrants should assess the available human, animal and alternative data.
There are many types of effect data

- Read Across
- (Q)SARs
- Endpoint Information: Annexes V-IX
  - Waiving: technical, exposure
  - Last resort
- In vitro
- Existing information
- In vivo TESTING
ITS under REACH

- In the Integrated Testing Strategies (ITS), provided in the Regulation and in the relevant guidance, the step-wise consideration of all relevant data is described.

- This may lead to identification of testing needs in order to characterise the inherent toxic properties of a substance and to meet the information requirements.

- ITSs cover both general and specific rules of adaptation.
Conditions for non-standard data for REACH & CLP

- Results must be adequate for the purpose of classification and labelling and/or risk assessment

- Key parameters from the standard test are addressed, e.g. adequate exposure duration & route

- Adequate documentation and scientific justification for using non-standard methods
Adverse Outcome Pathways

- Better use of mechanistic information

- Provide a plausible, testable progressions of adverse effects at different levels of biological organization, e.g. molecule > cell > tissue > organism

- OECD AOPs aim to address the traditional *in vivo* endpoints hence facilitating acceptance of predictions from non-standard methods.

- Can be used as a framework to develop integrated testing strategies (IToS) to assess particular toxicological endpoints.

- AOP based testing is expected to lead to results, which have high biological relevance and to IToSs that may replace the standard *in vivo* testing.
AOP Based testing strategy on Skin Sensitisation

- The OECD AOP for skin sensitisation has been finalized. It can serve as a framework for devising an ITS

- The individual assays will have limitations on the chemical structures they are valid for & limitations on the physical properties of the test materials

- The assays/blocks in the ITS and the overall assessment strategy needs to be validated and found suitable for a particular regulatory purpose

- It is important to decide on the purpose for the output prediction from the ITS; e.g. to replace the standard *in vivo* test and/or for potency assessment (for e.g. cosmetics.)

- ECVAM/IHCP are formulating a strategy & action plan for an alternative approach for skin sensitisation
The key biological mechanisms of the induction phase

- Ability of the chemical to **penetrate the skin** and reach the site of haptenation (skin bioavailability)

- Covalent **binding** of the chemical **to the skin protein** (haptenation)

- Release of **pro-inflammatory signals by epidermal keratinocytes**

- Activation and maturation of **Dendritic cells** (DC), the skin immunocompetent cells

- Migration of DC from skin to the **regional lymph nodes** and presentation of the antigen to T cells

- **Proliferation of memory T cells**
Skin sensitisation testing and the REACH registration deadlines

- The aspiration is to develop an integrated assessment strategy for skin sensitisation ready for the 2018 REACH registration deadline.

- Skin sensitisation (LLNA) is an Annex VII information requirement. It is likely that potentially many thousand industrial chemicals lack the skin sensitisation data.

- ECHA supports the development of the AOP based ITS and provide regulatory advice and support to the development.

- The aims is that the REACH registrants will be able to use a prediction scheme that can be used to fulfil the REACH registration information requirement for skin sensitisation for classification and risk characterization.
**Slide in reserve -- In vitro studies**

- Results from in vitro test may fully or partly replace an in vivo test if:
  - validated according to internationally agreed validation principles
  - results adequate for C&L, RA.
- The use of results from in vitro methods that have not yet been scientifically validated (“suitable studies”) depends on whether such study indicates certain dangerous property and on the potential risk identified.

**In vitro studies**

- Genotoxicity/Cytotoxicity
- Dermal absorption
- Irritation (skin – eye), phototoxicity
- Cellular metabolism/mechanism of action
- Macromolecular binding
- Sperm motility/Embryo culture
- The validation of in vitro tests to address skin sensitization is ongoing