ECHA's experience on use of non-animal methods for skin sensitisation

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Alternatives for Skin sensitization testing and assessment: a joint Cefic-LRI / Cosmetics Europe / EPAA workshop

Outline

- Information requirements under REACH and possibilities for adaptations
- Information submitted
- Use of adaptations and alternatives
- Potential use of *in vitro* methods

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REACH, Annex VII, section 8.3

- An *in vivo* skin sensitisation study is a standard information requirement.
- LLNA assay (EU method B.42/OECD TG 429) is the first choice of assay where it is justified that a new *in vivo* test is necessary → use of another method shall be justified.
- Before conducting the study the registrant has legal obligations to
  - Assess the available data (animal and/or human);
  - Consider specific rules for adaptation (column 2);
  - Consider alternative methods e.g. read-across, WoE, *in vitro* etc. (Annex XI adaptation possibilities).

Adaptation possibilities (column 2 of Annex VII, 8.3 and Annex XI)

- Column 2 i.e. specific rules for adaptation
  - Available information indicates that the substance should be classified for skin sensitisation or corrosivity (Note: If a corrosive substance is used in non-corrosive concentrations, sensitisation potential should be considered);
  - Substance is a strong acid (pH < 2.0) or strong base (pH ≥ 11.5);.
  - Substance is spontaneously flammable in air at room temperature.
- Annex XI i.e. general rules for adaptation
  - Use of existing data, weight of evidence, QSARS, *in vitro* methods, read-across or grouping and/or combinations of these.

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ECHA' s experience on skin sensitisation endpoint

Information submitted

- Statistical analysis performed for the report "The use of alternatives to testing on animals for the REACH Regulation" (Article 117(3) report), on registration dossiers available 1 October 2013.
  - 3813 dossiers for substances ≥ 100 tpa, 8521 endpoint study records (ESR) were submitted.
  - Experimental studies 4289, read-across 2130, weight of evidence 1328, (Q)SARs 83, study omitted 544, miscellaneous 147.
  - 54 *in vitro* studies were provided by registrants in their dossier by 1 October 2013 (only 4 *in vitro* studies identified in the previous Art. 117(3) report published in 2011).

Information submitted (2)

- A limited search of the registrations available by March 2015 revealed that since October 2013 more *in vitro* data for sensitisation has been submitted, albeit in small numbers (ca. 90 endpoint study records so far).
- Based on this search (studies submitted not evaluated) the submitted information consisted of
  - Only *in vitro* data provided for the endpoint.
  - *in vitro* data together with e.g.
    - Read-across
    - Old *in vivo* data
    - QSARs

ECHA's experience on use of adaptations

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Use of adaptations and alternatives

- The registrants do make use of column 2 adaptations e.g. based on corrosive nature of the substance
- Annex XI adaptations are frequently used
  - Read-across used often – ca. 25 % of the information submitted for skin sensitisation,
    - used either in one-to-one read-across or in a category approach;
    - or together with supporting evidence e.g. (Q)SARs and/or human data in a Weight of Evidence approach.

Problems observed in use of adaptations

- Read-across
  - Justification often missing or not adequate (too general and endpoint characteristics not considered).
  - Read-across must be, in all cases, justified scientifically and documented thoroughly.
- (Q)SARs
  - Only indication of results and software used, without providing QMRFs or QPRFs
    - Impossible to evaluate the results.
    - The structural characteristics of the registered substance should be covered by the training set of the QSAR model.

Potential use of *in vitro* methods

- Registrants have the obligation to consider the use of alternatives to animal testing (e.g. Annex VI guidance note and Art. 13(1)).
- REACH allows the standard information requirement to be adapted with use of *in vitro* methods either alone (Annex XI, 1.4) or within a Weight of Evidence Approach (Annex XI, 1.2) depending on the scope of the *in vitro* method.
- There are already internationally adopted and validated non-animal testing methods available for skin sensitisation that can be used for REACH purposes.
- There are also other non-animal testing methods available under various steps of development.
- As the *in vitro* methods are not stand-alone methods and have known limitations, information from several tests should be used within a Weight of Evidence approach.

Potential use of *in vitro* methods (2)

• As the use of the *in chemico/in vitro* methods in combination is in its early days, advice to the registrants needs to be provided especially having the 2018 registration deadline in mind.

• ECHA's web section on newly adopted OECD and EU test methods will be updated shortly to give advice to the registrants how these non-animal testing methods could be used for REACH purposes.

• Detailed guidance on how to use non-animal approaches will be described in the update of ECHAs R.7a guidance document for which the planned publication date is by summer 2016.

Conclusions

- LLNA seems to be currently the most commonly used animal test method for skin sensitisation.
- Registrants have used the adaptation possibilities either according to column 2 or Annex XI, including non-animal approaches.
- A tendency towards using *in vitro* data has been observed based on the studies submitted by registrants.
- Advice on the use of these non-animal approaches will be given to registrants.


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Thank you