TOXMINDS
Product Safety & Regulatory Affairs

Consortium/SIEF Approaches to Skin Sensitization Assessments

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Outline

Information requirements under REACH

- Described in REACH Annexes VI to XI
- Column I of Annex VI informs of standard requirement for skin sensitization for substances produced/imported in quantities ≥ 1tpa
  - Step 1: Assessment of all of the available human, animal and alternative data
  - Step 2: In vivo testing
- Step 2 does not need to be conducted if the substance of concern
  - Should be classified as skin sensitizer or corrosive
  - Is a strong acid (pH < 2) or base (pH > 11.5)
  - Is flammable in air at room temperature

Evaluation of information on skin sensitisation under REACH

- For hazard identification and dose response assessment, it is important to consider adequacy and completeness of the data
  - Adequacy assessment shall address reliability and relevance of the data;
  - Completeness refers to the conclusions on the comparison between available adequate information and information requirement under REACH;
- Conclusions rely on Weight of Evidence (WoE) approaches as categorized in REACH Annex XI section 1.2 based on methods used
  - Guideline and non-guideline tests;
  - 'Other types' of information justifying adaption of the standard testing regime

Types of human and animal data used for REACH registrations

- Human data on skin sensitisation
  - Epidemiological data, case reports and human experience (consumer, workers);
  - Diagnostic clinical tests (e.g., patch tests, repeated open application tests);
  - Confirmatory clinical or experimental studies (e.g., HRIPT, HMT)
- Animal data on skin sensitisation
  - LLNA (OECD TG 429; 'REACH-preferred method')
  - Guinea pig maximisation test or Buehler test (OECD TG 406) – generation of new GP testing for REACH registration purposes only if scientifically justified
  - Non-guideline tests (e.g., GP Draize or optimisation test, mouse ear swelling)

‘Alternative data’ used for REACH registrations

- Non-testing approaches to fill data gaps for skin sensitisation
  - Reaction chemistry, metabolism, bioavailability – structure activity relationship models (e.g., DEREK, OECD Tool Box);
  - Analogue based assessments (‘read-across’);
  - Chemical grouping/categories (interpolation, extrapolation)
- *In vitro* approaches
  - No officially adopted EU-OECD method *in vitro* test for skin sensitization exists; current approaches being explored and may be used in combination:
    - Chemical reactivity (e.g., protein binding/peptide reactivity assays);
    - Cell-based assays (e.g., expression of surface markers and/or cytokine release)
    - Epidermal bioavailability (i.e., dermal penetration is a pre-requisite for skin sensitisation)

(My) Overview of Consortia/SIEF Approaches

In a nutshell…all tools are being used!

- Typical approach for addressing skin sensitization endpoint in the case substance specific data on skin sensitization do NOT exist
  - Step 1: SAR analysis substance of interest (SOI)
  - Step 2: Identification and categorization of suitable structural analogues, assessment of adequacy of analogue data and applicability of non-testing approaches (e.g., grouping, read-across approach)
    - 'Suitability evaluation': chemical structure and reactivity (e.g., commonality of structural alerts, functional groups or double bonds), physico-chemical properties, bioavailability and metabolism
  - Step 3: Weight of evidence analysis leading to use of a non-testing approach to meet REACH requirements or further testing
    - Further testing: either *in vitro* or *in vivo* (LLNA or GPMT)

Case study I: Interpolation of data through grouping

- Example: Surfactant class with varying Alkyl chain length (i.e., Surf-C_8, Surf-C_{8-10}, Surf-C_{12}, Surf-C_{12-14}, Surf-C_{16-18})
- Available data/information
  - Negative LLNA for Surf-C_8, Surf-C_{12}, Surf-C_{16-18}
  - Absence of structural alerts for skin sensitization and/or protein reactivity (DEREK, OECD Toolbox)
  - Surfactant group generally meets REACH grouping criteria: common constituents/chemicals and functional groups, incremental change of PC properties across category, common metabolism;
  - Skin irritation potential decreases with increasing alkyl chain length (but no corrosivity of Surf-C_8)
  - Long-term use of all surfactants in consumer products with significant skin contact and no market reports of skin sensitisation effects
- Conclusion: No further testing necessary; lacking data for Surf-C_{8-10} and Surf-C_{12-14}, are being read-across to existing data within the group (interpolation)

Case study II: Identification of sensitisers w/o *in vivo* testing

- Example: Group of complex acrylate-based UVCBs; substances are structurally similar but as a result of different starting materials and process conditions differ slightly with regard to oligomerization degree and chain length
- Available data/information
  - Positive LLNA studies for some, no animal data for others;
  - Structural alerts for skin sensitization
  - Acrylate-based group generally meets REACH grouping criteria: common constituents/chemicals and functional groups, incremental change of PC properties across category, common metabolism;
  - Substances are only mildly irritating to skin;
  - No human data
- Conclusion: No further testing; all substances of the group were considered skin sensitizer and appropriate RM management measures proposed

Case study III: Discordant *in vivo* results and WoE-based assessment

- Example: Polyfunctional silicone type substances slightly differing in MW, viscosity and a single functional group
- Available data/information
  - 4/5 substances weakly positive in the LLNA (no dose response); 5/5 substances negative in the GPMT (high dose);
  - SAR analysis did not reveal a structural alert for skin sensitization for 4/5 substances; for one substance one path of reaction chemistry (activation) may explain some weak activity; neither study quality nor other chemical factors could explain the discordancy of the data;
  - LLNA studies included ear thickness measurements to determine degree of irritation; except for one substance which was tested positive in the LLNA, only a very low level or irritation was determined;
  - Absence of occupational allergic contact dermatitis; no in-market issues with structurally similar polyfunctional silicones used in cosmetic products
- Conclusion: WoE suggests that none of the examined silicone materials presents a skin sensitization hazard; the GPMT appears to provide more reliable results for identifying the skin sensitization hazard for this chemical class

Summary

- Consortia/SIEFs generally apply all tools and look at all suitable data that are available to address the skin sensitisation endpoint;
- Non-testing approaches such as (Q)SAR, grouping and/or read-across is extensively used to avoid unnecessary animal testing;
- Further *in vitro*, but sometimes also *in vivo,* testing may be necessary to confirm or identify the existence or absence of skin sensitisation properties;
- The type of chemistry often determines which tool is more suitable for skin sensitisation assessment. Hence, it is important to have all tools available;
- A weight of evidence approach is required for assessment of discordant skin sensitisation data sets.

Thank you for your attention!

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