C&L Framework, REACH and Skin sensitising potential

Nicholas Ball

Topics

- C&L framework
- Testing under REACH
- Weight of Evidence approach to classification

Issue

- C&L frameworks are fairly clear on classification for sensitising potential
- Consequences of classification can be severe
- Data requirements for REACH are explicit
- However, what if the prescribed assay appears not to represent the hazard of your test material?
- Could lead to an inappropriate classification
- How can this be avoided or dealt with?

The Classification and Labelling Framework

- 2 frameworks – Dangerous Substances (Preparations) Directive; Classification, Labelling and Packaging Legislation
- Criteria for classification as sensitiser are the same for DSD and CLP
  - CLP formalises concept of potency for setting specific concentration limits (moderate, strong, extreme – but no weak?)
- New ECHA guidance available on how to apply CLP
  - Covers weight of evidence, use of non-testing methods, discusses animal and human data

The Classification and Labelling Framework

- Positive classification as sensitiser requires:
  - 1 positive, well conducted/reliable animal test
  - Or compelling human evidence
- Negative data in humans (studies or experience) do not *normally* overwrite positive animal data
- Confounding results (animal/animal, or animal/human) are to be reconciled by assessing the quality of the data
- Weight of evidence approach to assessing data is encouraged

The Classification and Labelling Framework

- Overall aim of C&L is to inform workers/consumers about a hazard
- Allows hazard identification & appropriate risk management
- Correct classification is therefore very important
- Precautionary classification is not ideal and not consistent with a weight of evidence approach

Testing for REACH

- Sensitisation Data requirement listed in Annex VII, i.e. >1 t/ annum.
- Required prior to submission of registration dossier
- Very few possibilities for waiving sensitisation test e.g. for corrosive substances
- Should consider QSAR, read across, in vitro?
- For new data generation, the LLNA is the preferred method
  - generally considered that animal welfare and the quantitative, less subjective nature of the results drive the choice

Testing for REACH

- Other approved tests (GPMT/Buehler)
  - ONLY with “exceptional circumstances” where “scientific justification” supports the use of a test other than the LLNA
  - No guidance exists today that expands on what justification would support use of a method other than the LLNA
  - Without guidance on what justification is acceptable, it is difficult to build a case
- Existing human data OK; New human studies should not be conducted

Weight of Evidence Interpretation

- LLNA and Guinea Pig assays are considered to be acceptable for assessing skin sensitising potential
- LLNA is formally validated
  - but this exercise compared its predictivity to existing data from Guinea Pig assays and human data
  - The LLNA was found to be as predictive as the Guinea Pig assays – does this mean the Guinea Pig assays are also validated?
    - Yes, but a ‘formal validation’ has never been done
- The LLNA assesses induction, the Guinea Pig assays/ human patch tests assess elicitation;

Weight of Evidence Interpretation

- Human data varies widely – from well conducted patch test studies to general experience from consumer/industrial handling of products
- Additional data on protein reactivity, dermal penetration, structural alerts complement a WoE approach

Factors influencing a Weight of Evidence Interpretation

- In many cases only one animal assay will be available and perhaps some QSAR/read across information from similar substances
  - For existing substances, available data come predominantly from Guinea Pig assays
  - For new substances – the LLNA
- Certain chemistries such as Surfactants, LLNA and GPMT data often contradictory - Which assay is ‘correct’ or most relevant to humans?
- Validating the LLNA identified Sodium Lauryl Sulphate as a ‘false positive’.
  - **Decision based on weight of evidence**
  - ***If Sodium Lauryl Sulphate was a new substance and only tested in the LLNA, it would be considered as a sensitiser***

Factors influencing a Weight of Evidence Interpretation

- Acknowledged that there are false positives and negatives in the LLNA (metal salts) and GPTs (Ammonium thioglycolate), what is the mechanism?

- New published literature indicates how to identify false positive/negative results, but still very difficult to make a case without additional data.
  - ***Is it ethical to conduct a second assay to confirm or dispute an existing assay?***

- Reluctance to conduct multiple tests due to welfare considerations – does one negative test overrule a positive test or visa versa?
  - If not, what else is needed?

Factors influencing a Weight of Evidence Interpretation

- The GP assays also have deficiencies
  - Doses often lower than LLNA – No dose Response
  - Variety of historical protocols
  - ‘older data’?
  - Intra-dermal induction considered extreme in the past
  - Subjectivity of response
    - ‘how red do they look?’ ‘does that look like swelling to you?’
    - Limited quantitative data
  - Re-challenge not always done in ambiguous cases
- Human data from patch tests – low doses, small groups sizes
- Human data from experience – wide variability in reporting
  - ***Is lack of evidence in humans (i.e. no adverse reports) the same as evidence of no effect?***

Factors influencing a Weight of Evidence Interpretation

- In many cases there will be insufficient data to make a robust judgement
- In order to use weight of evidence to determine an appropriate classification, you need more than one data point
- Only option is to rely on the results of the one assay that gives highest cause for concern

What do we need

- In order to derive the ‘correct’ classification
  - Guidance on when certain tests are inappropriate – Applicability domains
  - Additional insight into what causes ‘false’ results (positive or negative) in assays and their relevance with respect to human reactions
  - More tools to enable a weight of evidence case to be constructed
- Pragmatism in classification

Thanks for your Time!