IDEA

International Dialogue for the Evaluation of Allergens

Hazard assessment: integration of non-animal data into the QRA

Prof Jim Bridges

Chair, IDEA Supervisory Group

Annual Review 2019 ● European Parliament ● 25 February 2019

Utilisation of existing non-animal *in vitro* tests in the framework

Input to the framework:

- Identify the potential of the Fragrance Ingredient (FI) to induce an allergic reaction.
- Evaluate the potency of the FI against established reference standards

Test design:

The tests available to date are based on the major three stages in the adverse outcome pathway (AOP) namely:

KE1 Covalent binding to proteins

KE2 Activation of keratinocytes

KE3 Activation of Langerhans and dendritic cells

Questions to be addressed
a. Test selection

i) The LLNA test covers the first four steps in the AOP. Currently in vitro tests are only available for the first three. Is this of concern?

ii) Do we need to use entirely separate tests for KE1, KE2 and KE3 for hazard identification?

iii) Do the tests above also permit potency characterization for risk assessment?

Questions to be addressed
b. Test conditions

i) Does the test preparation have suitable xenobiotic metabolism activity?

ii) Are suitable reference standards available for comparative potency assessment? Should they be selected according to the chemical class of the FI ?

iii) How should the FI be applied (e.g. solvent selection)

In vitro tests: determination of potency

Working definition of potency

The potency of induction (as previously identified by the Local Lymph Node Assay (LLNA)) in mice.

Concept

An intrinsic property of a sensitising substance. It is likely to reflect a chemical and biologically dependent continuum and to vary widely between FIs.

Challenges

Skin sensitisation potency depends on a number of factors e.g. the quality and breadth of response of T-lymphocytes, which are difficult to measure in vitro.

In vitro tests for potency assessment: views expressed at Dec 2018 workshop

- Measurements of hazard do not necessarily contribute to the assessment of potency
- Markers of potency should be causally related and quantitatively associated with the relevant endpoint –acquisition of allergy
- Better evaluation of protein haptenization is needed (kinetics/amino acid selectivity/orientation of hapten expression)

Suggestions on other endpoints to evaluate potency of a FI

- Gene expression/epigenetic/proteomic signatures
- More detailed investigation of the response of dendritic cells (KE3)
- Measurement of other danger signal responses

Combining findings from all sources

Issue

Should the same weighting be applied to the findings from each test or should some tests justify a higher weighting?

Methodology already in use

Bayesian networks and artificial neural networks are already being applied to combine the findings. The use of artificial intelligence was proposed. How should the pros and cons of each be compared?

Selection

Should there be a methodology for applying a Weight of Evidence approach?

General

How can transparency be ensured?

Non-animal tests: next steps?

- Identify criteria for the chemical reference standards to be used for test evaluation and potency comparison purposes.
- Review the approaches for exposure of the fragrance to in vitro systems
- Provide a platform for further evaluation of whether it is essential to use test findings for each step in the AOP
- Assess the allowance needed for uncertainties in extrapolation of test findings to derive human NESIL values
- Develop a utilisable Weight of Evidence methodology rule set for combining the relevant information sources